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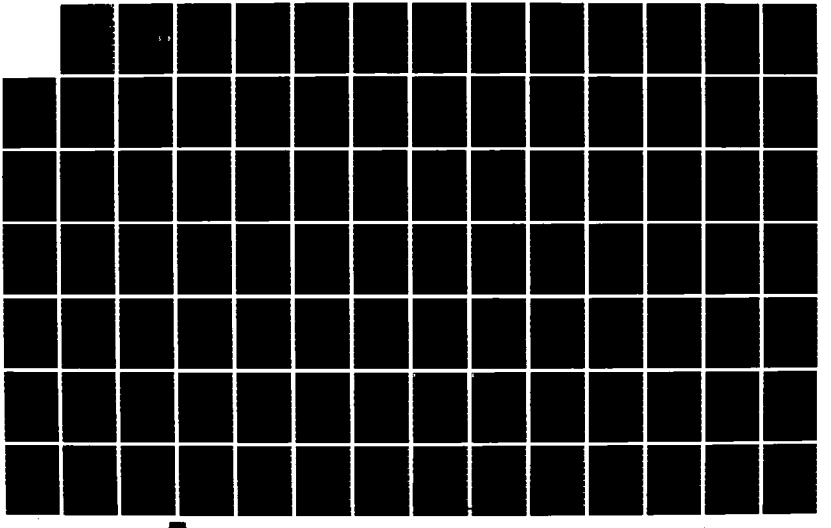

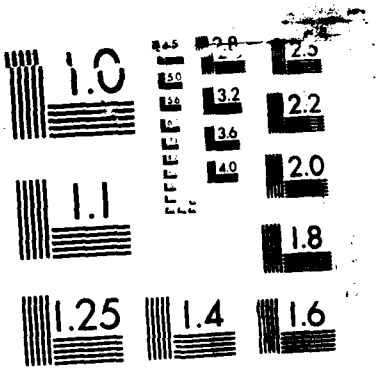

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REPORT NUMBER 3

"Investigations Regarding Anesthesia During Hypovolemic Conditions"

Annual Summary Report

Richard B. Weiskopf, M.D.

25 September 1983

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

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This research attends to unmet requirements in the physiological management of moderately and severely wounded soldiers, thereby (a) improving the return-to-duty rate of the combat-injured, (b) reducing morbidity and mortality of the combat-injured, and (c) reducing resource (primarily material and logistical support) utilization by Army medical field facilities. The research examines the interaction of anesthetic agents appropriate for use in a combat environment with hemorrhage. In doing so, the physiology of hemorrhage the physiological

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processes that contribute to the differences among anesthetic agents for induction and maintenance of anesthesia during hemorrhage will be examined. Swine are used as the experimental model, examining the rationale and physiology of use of nitrous oxide, enflurane, isoflurane, halothane, thiopental and ketamine for induction of anesthesia during the hypovolemic condition.

We have found swine to be an excellent laboratory model for the study of hemorrhage, and the interaction of anesthetic agents with hemorrhage. We have characterized the awake swine response to hemorrhage, and defined the swine's blood acid-base chemistry. During hypovolemia, induction of anesthesia with either ketamine or thiopental causes similar, important deterioration of cardiovascular compensation for moderate hemorrhage. Reductions in systemic vascular resistance, mean blood pressure, and cardiac output are not different in hypovolemic animals in whom anesthesia is induced with thiopental in comparison with those in whom anesthesia is induced with ketamine. Both agents also further exaggerate the lactic acidosis seen with hemorrhage. A potentially important difference between the two agents is the continued progressive lactic acidosis one half hour after induction seen in ketamine induced animals, but not in thiopental induced animals. We conclude that induction of anesthesia in hypovolemic condition with ketamine does not offer any advantage over induction of anesthesia with thiopental in a similar circumstance. Similarly, enflurane, halothane, and isoflurane when used for induction of anesthesia in hypovolemic swine all cause deterioration of cardiovascular compensation for hemorrhage. The decrease in systemic vascular resistance, cardiac output, and mean systemic blood pressure among the animals receiving the three inhalation agents are quite similar, as are the metabolic sequelae and increased acidosis. We have found that 30% hypovolemia decreases the minimal anesthetic requirement of ketamine and thiopental equivalently, approximately 35-40%. We have determined the minimal alveolar anesthetic concentration (MAC) in swine for halothane (1.25%) and nitrous oxide (277%). We have found than when nitrous oxide is used for induction of anesthesia during moderate hypovolemia, rather than resulting in stimulation, it causes deterioration of cardiovascular compensation and lactic acidosis similar to that seen with other inhalation anesthetic agents. Subsequent recovery appears to be more prominent with nitrous oxide than with other inhalation anesthetic agents. We have found that in awake moderately hypovolemic swine the renin-angiotensin system does not appear to have an important compensatory role. This may not be the case during anesthesia.

The products of this project are important and meaningful data and recommendations to be provided USAMRDC, AHS, and ultimately the user--the anesthetist in a combat environment--regarding the use (potential advantages and disadvantages) of anesthetic agents for acutely injured soldiers.

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3. Summary

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4. FOREWARD

In conducting the research described in this report, the investigator adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

5. Table of Contents

6. List of Tables and Figures

7. Body of Report

A. Background:

1. Overall Objectives:

The long-term objectives of this research project are to improve the physiological management of moderately and severely injured soldiers, and thereby (a) improve the return-to-duty rate of the combat-injured, and (b) reduce morbidity and mortality of the combat-injured. Certain portions of the project also focus on attempts to reduce resource (primarily material and logistical support) utilization required for accomplishment of (a) and (b) above.

This research examines the interaction of anesthetic agents, appropriate for use in a combat environment, with hemorrhage. In doing so, we also attempt to define the physiological processes that contribute to the differences among anesthetic agents during hemorrhage and the differences between the physiological effects of anesthetics during normovolemia and during hypovolemia. It is hoped that improved management will result from such an understanding.

2. Introduction:

Further advances for forward resuscitation and in management of the combat-wounded will depend, in part, on the acquisition and application of physiological principles and understanding of the interaction of anesthetic agents and techniques with physiology and pathophysiology.

Within the past twenty years, there has been a vast proliferation of research in anesthesia and anesthesia-related fields. Despite the information gained, the paucity of knowledge upon which anesthesiologists must base crucial, life-determining decisions regarding the anesthetic care of the acutely wounded soldier is distressingly evident in the chapter on "Anesthesia and Analgesia" of the First US Revision of the Emergency War Surgery NATO Handbook (2). The NATO handbook quite accurately reflects, "In the wounded who require surgery, the most significant alterations in physiology involve the circulatory and respiratory systems." The anesthesiologist in a combat environment, in order to be able to make the intelligent, informed decisions for the proper care of his patient, must have the knowledge of the appropriate normal physiology, abnormal pathophysiology, and how both are altered by the drugs, agents, and techniques he may utilize.

In addition to ensuring adequate ventilation and gas exchange, the anesthesiologist must also be concerned with optimizing cardiovascular function and selecting agents and techniques that will provide the appropriate alterations in cardiac output, peripheral vascular resistance, total body oxygen consumption, systemic blood pressure, myocardial work, myocardial oxygen consumption, and pulmonary vascular resistance. Lacking the ability to create appropriate alterations, he should, at the worst, have the ability to select the agents and techniques that will do the least harm. Myocardial, cerebral, and peripheral tissue blood flow must be maintained at levels sufficient for aerobic metabolism.

All anesthetic agents have profound influence on all the variables listed above. Halothane, fluroxene, diethyl ether, and cyclopropane, in normal, healthy, young male human volunteers, all elevate mean right atrial pressure, increase skin blood flow and decrease oxygen consumption and base excess (3-11). Ether, fluroxene, and cyclopropane cause minimal or no decrease in cardiac output, stroke volume, left-ventricular work, stroke work, and mean arterial pressure (5). Halothane, fluroxene, and ether decrease total peripheral resistance, while cyclopropane significantly increases it. Unlike other anesthetic agents, deep fluroxene anesthesia causes a rise in arterial pressure (3-5) as a result of increased central sympathetic outflow (12).

Enflurane during spontaneous ventilation results in increased P_aCO_2, greatly decreased systemic vascular resistance, reduced mean arterial blood pressure and stroke volume, but an increased heart rate and cardiac output (13). The investigators attributed the latter to be a result of "beta-sympathetic-like-stimulation" in response to elevated arterial PCO_2 concentrations. When ventilation is controlled so that PCO_2 is normal, cardiac output decreases in comparison with the awake state.

Isoflurane, a relatively new inhalational agent, which has been released recently by the FDA for noninvestigational use, has been shown in unpremedicated, healthy young male volunteers to preserve cardiac output unchanged, decrease stroke volume, arterial pressure, peripheral resistance, $\dot{V}O_2$ and left-ventricular work, while increasing right atrial pressure and $\dot{Q}/\dot{V}O_2$ during constant P_aCO_2, maintained by controlled ventilation (14). During spontaneous ventilation, cardiac output and heart rate rise further as a result of rise in P_aCO_2, despite the blunting of the cardiovascular response to CO_2 by isoflurane (15).

Nitrous oxide, first prepared by Priestly in 1772, and first demonstrated to have anesthetic properties by Sir Humphrey Davey in 1800, is not sufficiently potent for sole use as an anesthetic agent. Hyperbaric studies have demonstrated that at normal barometric pressure approximately 110% N_2O would be required to produce anesthesia. Nevertheless, N_2O is almost universally added to other inhalation agents to reduce the concentration of the other inhalation anesthetic. The rationale for this practice was originally related to the now-discarded belief that N_2O, beyond its analgesic/anesthetic properties, had no other pharmacological actions. Within the past 10-15 year information has been gathered regarding cardiovascular actions of N_2O in experimental animals as well as in man. Because of the wide variations in experimental designs, the results are not clear. Many variables appear to influence greatly the cardiovascular action of N_2O, e.g., type of ventilation, prior administration of drugs, background anesthetic agent, duration of administration of N_2O prior to measurement, patient age, and patient physical status. Smith et al (16) also suggested (without supporting evidence or citation of any references) that the "extent of ... trauma or blood loss" probably influences the cardiovascular action of N_2O. When added to halothane, N_2O appears to result in cardiovascular stimulation in normal man (17,18), in cardiac patients (19), and in the normal dog (20-22), although Hill et al (23) noted cardiovascular depression with the addition of N_2O to halothane in patients with heart disease (for operation for aortic or mitral valve replacement or coronary artery bypass graft), and Brower and Merin (24) failed to note significant cardiovascular action of N_2O upon its addition to halothane anesthesia in swine. Stimulation is seen in man with the addition of nitrous

oxide to fluroxene (25), diethyl ether (26), and isoflurane (27) anesthesia. In contrast, Smith et al (16) recently observed minimal cardiovascular changes with the addition of N_2O to enflurane anesthesia. With the addition of N_2O to a background of narcotic anesthesia, cardiovascular depression is frequently noted in man (28,29) and in dogs (30).

Cardiovascular stimulation in man by the addition of N_2O to all inhalation anesthetic agents except enflurane is likely an indirect effect. Nitrous oxide was previously thought to spare the myocardium of depression and cause a minimal peripheral vasoconstriction (31-33), probably through an increase in sympathetic activity (32). Recent work has demonstrated a direct decrease in myocardial contractile force by 50% N_2O (34). This is not as great a reduction as caused by an equipotent anesthetic concentration of halothane (34.35). In in vivo studies, the stimulation of sympathetic nervous activity by N_2O would tend to antagonize the direct myocardial depression (36,37).

Despite the stimulation seen, it appears that N_2O does not enhance the overall margin of safety of inhalation anesthetic agents with respect to the amount of agent required to produce respiratory or cardiac arrest (38). Nevertheless, N_2O continues to be used ubiquitously unless the patient physiologically requires very high concentrations of inspired oxygen.

The stimulatory response requires a system capable of providing a relatively intact sympathetic response. This may be neither true nor desirable during hypovolemia. This consideration does not appear to have been tested.

With the introduction of thiopental, induction of anesthesia by intravenous anesthetics became popular. With the entry of the U.S. into World War II, much debate, based on anecdotal experience, arose regarding the wisdom of the use of thiopental in a military setting (39-50). The predominant opinion appears to have been that thiopental should not be used for induction of anesthesia in cases of severe trauma or shock (43,45). However, anesthetic practice today differs greatly from that employed in the early 1940's. At that time, supplemental oxygen was not administered to all patients; nor was it even available on a routine basis. Patients breathed spontaneously. The doses of thiopental that were employed (minimum of 0.5 grams; most often several grams) are by today's standards, grossly excessive, especially for patients with abnormal hemodynamics.

Although thiopental did become the subject of research centered on its hemodynamic properties indicating myocardial depression (51) and reduction of vasomotor tone (52), its use for induction during hypovolemia has not been studied systematically.

More recently, a relatively new agent, ketamine, has been advocated for use in hypovolemic shock (53). In doses of 2 mg/kg IV, given to fit patients without premedication, ketamine has been shown to increase heart rate 36%, systolic blood pressure 41%, diastolic blood pressure 40%, mean arterial pressure 40%, cardiac output 57%, and stroke volume 22% (54,55). This effect is probably mediated through vagolytic activity through baroreceptor blockade (56-58) and central adrenergic stimulation with peripheral alpha effect (56,59-62). Low doses (1-2 mg/kg IV) result in a variable positive inotropic effect (63,64), whereas high doses are negatively inotropic (65-67). Unfortunately, ketamine is relatively short-acting (20-30 minutes), and repeat injections have been reported to have less or no pressor response (54,68,69).

Premedication with atropine attenuates the cardiovascular response to ketamine (70-73). When ketamine is given during general anesthesia, a depressor response is elicited (74-76).

Ketamine has been used as an induction agent for hypovolemic shock. In dogs, Virtue et al (67) noted a modest (4%) increase in blood pressure, and Gassner et al (77) noted an increase in blood pressure and heart rate in hypotensive cats on induction with ketamine. These studies, however, did not quantitate the degree of hypovolemia. In 30 humans in "hemorrhagic shock", Corssen et al (78) reported a 17% increase in systolic blood pressure upon induction with an unspecified dose of ketamine. Chasapakis et al (79) noted a similar response in 13 similar patients premedicated with atropine and given 2 mg/kg IV and pancuronium 4 mg IV for induction. Unfortunately, none of these quantitated the degree of hypovolemia not commented upon continued intraoperative course; nor did they compare ketamine with other agents. Most of this literature regarding ketamine has been of less than good quality.

During the past year, etomidate, has been released for use in the United States. Etomidate is a rapidly acting, potent hypnotic of short duration of action. It is a carboxylated imidizole, synthesized in 1965, used in Europe for several years, but only just released for use in the United States. Etomidate induces anesthesia rapidly, with minimal cardiovascular changes in normal animals (209-213) and man (214-216). It has been reported that in patients with cardiopulmonary disease, etomidate causes minimal decreases in arterial blood pressure and peripheral resistance (215,217). Thus, it has been suggested as a valuable induction agent "in patients with little or no cardiac reserve" (218). The agent is currently marketed in the United States by Abbott Laboratories, who claims that it "may be particularly useful for ... patients in shock ..." (219). This claim could not be substantiated by the medical department of Abbott Laboratories (220) who could only provide three references for use of etomidate for emergency anesthesia during hemorrhage, all of which refer to a single anecdotal incident (221-223).

These claims are not dissimilar from those made for thiopental upon its intruction in the 1930's. Then, prior to appropriate studies, at the outset of the United States' involvement in World War II, thiopental was used for induction of anesthesia in hypovolemic sailors and soldiers, with tragic results (39-50). Etomidate should be evaluated for its effects when used for induction of anesthesia during hypovolemia.

With the exceptions noted, the pharmacology described above was learned from anesthetizing either normal animals or normal, young, healthy men. It is inappropriate to attempt to translate these pharmacological findings from normal man to hypovolemic man. Many of the indirect but important cardiovascular actions of anesthetic agents, especially those of enflurane, isoflurane, nitrous oxide, and ketamine, require an intact sympathetic response. Hemorrhage results in sympathetic discharge (90). Further sympathetic outflow may be neither possible nor desirable.

Only two studies have compared anesthetic agents during hemorrhage (81,92). Theye et al (81) compared survival times during removal of 0-40 $ml \cdot kg^{-1}$ of blood from dogs with intact spleens, ventilated and anesthetized with cyclopropane, halothane, or isoflurane. Prior to blood loss, cyclopropane resulted in higher cardiac output and mean arterial blood pressure than either halothane or isoflurane, presumably as a result of higher arterial

epinephrine concentration. With hemorrhage, cardiac output and mean arterial blood pressure fell more rapidly with cyclopropane than with either inhalation agent; arterial epinephrine increased more rapidly with cyclopropane than with either inhalation agent; oxygen consumption fell the most and arterial lactate concentration increased the most with cyclopropane. Survival time was shorter with cyclopropane than with either isoflurane or halothane.

We have compared, in splenectomized dogs, the cardiorespiratory influences of graded hemorrhage (0, 10, 20, and 30% blood loss) during enflurane, halothane, isoflurane, and ketamine anesthesia with spontaneous ventilation (82). Diethyl ether and cyclopropane were not studied because of their flammability and explosive potential and, therefore, impracticality in a battlefield medical facility environment. In comparison with the awake state during normovolemia, of the agents studied, only ketamine provided cardiovascular stimulation (increased heart rate and cardiac output), while enflurane resulted in the greatest depression of cardiovascular function (decreased mean arterial blood pressure, cardiac output, and stroke volume). With graded blood loss, cardiac output decreased more rapidly with ketamine than with all of the three inhalation agents, so that by 30% hemorrhage there was no difference in cardiac output among halothane, isoflurane, and ketamine. In response to hemorrhage, systemic vascular resistance increased most with ketamine. Thus, at 30% blood loss, mean arterial blood pressure was highest with ketamine. Rate-pressure product and minute work were highest with ketamine throughout hemorrhage except for minute work at 30% blood loss. This was reflected in total body oxygen consumption being highest with ketamine at 0-20% blood loss. Oxygen consumption did not change with hemorrhage with any inhalation agent, but decreased with hemorrhage with ketamine, suggesting that oxygen demand was not met; arterial blood lactate concentration increased with hemorrhage only with ketamine. Under these conditions of the experiments of Theye (81) and our own (82), sympathetic stimulation appears to be an undesirable property of an anesthetic agent when used for maintenance of anesthesia during moderate hypovolemia. These expriments (82) were performed while the dogs breathed spontaneously, and resulted in differing arterial PCO_2 among the anesthetic agents. Although the cardiovascular stimulation caused by carbon dioxide (15,82) is blunted by anesthetic agents (15,18,83,84), the varying levels of CO_2 among the agents may have influenced the results.

The renin-antiotensin (R-A) system also plays an important role in the physiologic response to and compensation for hemorrhage (86-91). The influence of anesthetic agents on the R-A system has received some attention, with conflicting results (92-98). However, under normal circumstances, the R-A system appears not to be an important controller of cardiovascular dynamics during anesthesia (97). This is not the case, however, in some specific circumstances of altered cardiovascular dynamics. When hypotension is intentionally created by vasodilation with nitroprusside in anesthetized animals, the R-A system plays an important role in preventing what would otherwise be a far greater fall in systemic blood pressure (i.e., it produces significant compensation) (99-100). The R-A system is also responsible for the rebound hypertension observed following discontinuation of nitroprusside (101-102). In sodium-depleted animals, the R-A system is an important regulator of blood pressure during anesthesia (103). These lines of evidence, indicating that anesthetic agents decrease blood pressure in states where the R-A system is activated, lead one to suspect that this may also be the case during

hemorrhage. Although this hypothesis has also been suggested by others (97), it does not appear to have been tested.

Understanding the interaction of anesthetic agents with the R-A system during hemorrhage offers the possibility of improved casualty management through appropriate selection of anesthetic agents and R-A stimulants or blockers.

Although the vasopressor activity of extracts of the pituitary gland was first observed 90 years ago (183), the role of vasopressin as an antidiuretic has received far more attention because that action occurs with far less amounts of vasopressin than does its pressor action (184-186). Research was further hindered by the use of insensitive, unreliable biological assay in anesthetized animals (180), until the development of a sensitive, reliable radioimmunoassay. Vasopressin is now recognized as the most potent vasoconstrictor yet studied (180). Only recently have investigations centered on the role of vasopressin in response to hemorrhage. Evidence that vasopressin has an important role in hemorrhage comes from several lines of evidence. It has been shown that plasma vasopressin concentration increases markedly in response to hemorrhage (187-190). Hypophysectomized dogs have an impaired ability to maintain arterial blood pressure following hemorrhage (191,192). Exogenously administered vasopressin resulting in plasma levels seen during hemorrhage can increase blood pressure (189,190,193,194). Pharmacological blockade of vasopressin in anesthetized spinal anflexic dogs impairs maintenance of blood pressure during hemorrhage to the same extent as does hypophysectomy (192). Most important, in unanesthetized dogs, Schwartz and Reid have demonstrated that blockade of vasopressin results in hypotension following mild hemorrhage, which without vasopressin blockade does not result in hypotension (181). Anesthetized rats genetically deficient of biologically active vasopressin (Brattleboro) (204-207) recover from hemorrhage less rapidly than do other strains of rats with active vasopressin. Chemical blockade of vasopressin in the normal anesthetized rat, likewise causes slower recovery from hemorrhage (207).

There have been no similar reports of investigations in unanesthetized, intact animals bled to a greater extent, sufficient to result in hypotension. Thus, the importance of vasopressin in compensation for moderate or severe hemorrhage is not known. We now have preliminary data which indicates that the role for vasopressin in compensation for moderate hemorrhage is of critical importance, and appears to be of greater importance than the sympathoadrenal or renal-angiotensin systems (195).

Despite the important role of vasopressin in cardiovascular regulation (180), little is known of the effects of anesthetics on vasopsressin secretion and action. Because of the uncertain effects of anesthetic agents on vasopressin levels, in a recent authoritative review of vasopressin's role in cardiovascular regulation, Cowley rejected all data obtained from anesthetized animals (180).

There have been several reports of vasopressin levels in man, during anesthesia, and surgery (196-200). Unfortunately all patients had significant cardiac disease, for which they were undergoing cardiac surgery. All groups were small in number, all patients had no fluid overnight, most were being treated with propanalol, all were premedicated with a variety of drugs, and the initial assessment of plasma vasopressin concentration was made after

insertion of venous, systemic arterial and pulmonary arterial cannulae. In most instances, anesthesia per se had no statistical effect on vasopressin levels, and only high-dose morphine, alfentanil, and sufentanil prevented an increased plasma AVP level with surgery. Of course, there were no controls consisting of patients undergoing surgery without any anesthetic, so it is not possible to determine if the other anesthetics attenuated the vasopressin response to surgery. These investigators were all interested in plasma levels of vasopressin as some sort of an indicator of "stress", and despite the now known importance of vasopressin in cardiovascular regulation, none calculated changes in systemic vascular resistance (they did occur as best as I can calculate from the data published) or discussed its importance.

Although these reports measured plasma AVP concentrations, there are no reports of experimental testing of whether anesthetic agents influence the cardiovascular actions of vasopressin.

There exists only a single report that concerned itself with the question of whether anesthetic agents alter vasopressin response to hemorrhage (202). Unfortunately, this work was performed before the advent of radioimmunoassay, and thus utilized an insensitive, non-specific, and unreliable biological assay. Furthermore, animals were first anesthetized and then bled. Thus, the effect of anesthetics on existing compensation for hemorrhage (the crucial question when inducing anesthesia in a hypovolemic individual) was not tested. Finally, none of the anesthetics tested (ether, pentobarbitol, urethane, chloralose, and ethanol) would be used today clinically.

Prior to the initiation of this contract there was no scientifically derived information regarding the actions of anesthetic agents when used for induction of anesthesia in a hypovolemic condition. The work described in this report represents efforts to delineate the interactions of anesthetic agents and cardiovascular control mechanisms and effects during significant hypovolemia.

B. Approach:

1. Comparison of ketamine, thiopental, enflurane, halothane, and isoflurane for induction of anesthesia during moderate hypovolemia.

Young domestic swine (Chester-White-Yorkshire mix breed; 18-21 kg) are being used to investigate the cardiovascular and metabolic response to induction of anesthesia during hypovolemia. We use swine because (a) dogs are becoming increasingly difficult to obtain for purposes of research; (b) swine are readily available in nearly uniform size; (c) the cardiovascular system of swine more closely resembles man than does that of the dog; (d) swine hemorrhage models have been used successfully by others. Although we were not aware of it at the initiation of this project, Hannon at the Letterman Army Institute of Research has had good results bleeding awake swine of approximately the same size we use (104-105). His animals have been bled by as much as 50% of their estimated blood volume while unanesthetized and unrestrained. von Engelhardt reviewed the cardiovascular parameters of swine, although much of the data was accumulated in anesthetized animals (106). Awake swine have been used to investigate renal blood flow at rest and during exercise (107), capillary flow during hemorrhagic shock (108), humoral response to hemorrhage (109-110), and myocardial metabolism after hemorrhage (111). The anesthetized pig has been used for a variety of studies, including hemorrhage (112-118), efficacy of stromal-free hemoglobin (119), and myocardial effects of anesthetic agents (120).

Our animals are first briefly anesthetized with an inhalation agent to allow for placement of peripheral venous, arterial, and thermistor-tipped pulmonary arterial cannulae. The trachea is intubated, the animal paralyzed and ventilated with a tidal volume of 20 ml/kg, and ventilatory rate adjusted to maintain arterial PCO_2 at 40 torr.

Inspired partial pressure of oxygen (P_IO_2) is adjusted to maintain partial pressure of oxygen in arterial blood (P_aO_2) at approximately 150 torr. The balance of inspired gas is nitrogen. End-tidal partial pressures of O_2, CO_2, N_2, N_2O, isoflurane, enflurane, and halothane are monitored at the endotracheal tube orifice by mass spectroscopy. The pig is paralyzed with metocurine, 0.2 mg/kg IV, and supplemented as required. Metocurine is used because of its lesser cardiovascular effects when compared with pancuronium, gallamine, or d-tubocurarine (121). A percutaneous venous catheter is placed in a forelimb, and a catheter is threaded through the superficial femoral artery into the abdominal aorta. A thermister-tipped, flow-directed, triple-lumen catheter is introduced percutaneously just above the suprasternal notch through the innominate vein into the pulmonary artery. Placement is verified by pressure trace and the ability to obtain pulmonary arterial (capillary) wedge pressure. Throughout these experiments, each swine's temperature (measured by the PA catheter thermistor) is maintained within $\pm$ 1 C^o of the animal's original temperature. Following placement of all cannulae and elimination of anesthetic agents by continued ventilation, measurements are made in the normovolemic condition. Samples are withdrawn from the femoral arterial and pulmonary arterial catheters for measurement of arterial and mixed venous blood gases, pH, and oxygen concentration. Blood gases are measured by Radiometer electrodes in Radiometer steel-and-glass cuvets; pH is measured with a Severinghaus-UC electrode (122), all thermostatically controlled at 37° C. Oxygen concentration is measured by an electrolytic cell (Lex-O_2-Con-TL)

(123). As an indicator of tissue oxygenation, blood samples are also withdrawn for the measurement of lactate and pyruvate concentrations. To assess each anesthetic agent's influence on the sympathetic response to hemorrhage, blood is sampled for measurement of total catecholamine, epinephrine, and norepinephrine concentrations (124). To assess experimental effects on the renin-angiotensin system, arterial blood is sampled for assay of plasma renin activity (125). Femoral arterial and pulmonary arterial blood pressures are continuously transduced by Statham 23Db transducers. Pulmonary arterial wedge pressure is measured by inflation of the balloon of the pulmonary arterial catheter. Right atrial pressure is measured via the proximal lumen of the same catheter. Cardiac output is estimated by a thermodilution technique, injecting 3 ml of 0° C 0.9% saline through the pulmonary arterial catheter, and using an analog computer (Edwards Laboratories Model 9520A). Electrocardiogram is constantly monitored.

The following variables are recorded on a multi-channel polygraph: partial pressures of oxygen, carbon dioxide, nitrous oxide, enflurane, isoflurane, and halothane at the tracheostomy tube orifice; femoral and pulmonary arterial blood pressures (phasic; mean pressures are electrically generated by the pre-amplifier; pulmonary arterial wedge pressure and right atrial pressure are recorded on the same channel as phasic and mean pulmonary artery pressure); electrocardiogram; thermodilution trace from the PA catheter thermistor--necessary to ensure that the washout is logarithmic and that the computer-derived cardiac output value is valid. From these measurements, the following are calculated: base-excess (126-127), stroke volume, mean arterial and pulmonary pressure, stroke and minute myocardial work, systemic and pulmonary vascular resistances, total-body oxygen consumption (cardiac output x $C_{a-v}O_2$), oxygen transport, and ratio of oxygen transport to oxygen consumption. Following these measurements, the pig is bled during a 30-minute period of 30% of its blood volume (106) through the arterial catheter into a transfer pack containing heparin so that the final concentration of heparin is 1 unit heparin/ml of blood. After a minimum of 30 minutes, all measurements are repeated. Thus, we evaluate each swine awake in the normovolemic condition, and following 30% hemorrhage.

Each pig is randomly assigned to one of the anesthetic groups listed below. With the animal hypovolemic, we then induce anesthesia with one of the following:

Group I: Control; no anesthetic agent administered

Group II: Enflurane, 1.25% end-tidal

Group III: Halothane, 0.50% end-tidal

Group IV: Isoflurane, 0.85% end-tidal

Group V: Nitrous oxide, 60% end-tidal

Group VI: Ketamine (for IV dose, see below)

Group VII: Thiopental (for IV dose, see below)

The concentrations of inhalation agents have been selected to be slightly greater than one-half the required minimal alveolar concentration in the normovolemic animal [hypotension reduces anesthetic requirement (128,154,155)]. The doses of injectable agents (thiopental and ketamine) are established in the following manner. Twenty-four to 48 hours before experimentation, with the pig (normovolemic) resting quietly in a sling, the amount of intravenous agent required to produce loss of lid and corneal reflexes and loss of response to ear-pinch is determined. The dose used for induction of anesthesia during hypovolemia is one-half the dose established during normovolemia 24-48 hours previously. Ear-pinch following induction with this dose during hypovolemia has failed to elicit any response.

End-tidal gas partial pressures, systemic and pulmonary artery pressures, and ECG are continuously recorded during induction. Qp, PAP_w, and RAP are measured every 5 minutes during induction of anesthesia.

All measurements, calculations, and blood samplings (as indicated above for the awake conditions) are performed at 5 and 30 minutes after induction of anesthesia. In this way, both the transient and quasi steady-state conditions are assessed.

Following these measurements, shed blood is returned, and after 30 minutes, all measurements, samplings, and calculations are repeated. Anesthesia is then discontinued and measurements and calculations repeated 30 minutes after the elimination of the anesthetic agent.

This experimental approach will allow us to show the influence of time (physiologic compensation, or deterioration, if any) on the preparation by comparison of data obtained during the course of experimentation within the control group, and by comparison, within each anesthetic group, of the awake normovolemic values prior to hemorrhage with similar values after return of shed blood and elimination of anesthetic agents.

The data will show the comparative cardiovascular influence of anesthetic agents used for induction of anesthesia during significant hypovolemia.

These results will allow us to provide recommendations to USAMRDC regarding choice of anesthetic agents for use for induction of anesthesia in a wounded soldier who is hypovolemic, and whose blood volume cannot be adequately restored prior to surgery.

Statistical Treatment of Data: Cardiovascular and metabolic variables among anesthetic agents and the control group will be compared using analysis of variance with repeated measures, and Neuman-Keuls method of multiple comparisons (129). Similar statistical tests will be performed to compare the awake hypovolemic with the anesthetized hypovolemic state, as well as the awake normovolemic with the awake hypovolemic state. These tests will be conducted as the series of experiments progresses, and the experiments will be terminated upon achieving statistical significance ($P < 0.05$) among anesthetic agents, thus affording the possibility of using fewer than the stated number of animals.

2. Swine blood acid-base chemistry:

In order to appropriately evaluate the metabolic sequelae of subsequent experimentation, we required information regarding swine blood acid-base chemistry.

We were unable to find this information in the literature. Although we lacked information indicating specific differences in acid-base parameters between human and experimental animal blood, we were not especially concerned until the report of Scott Emuakpor et al. (161), which indicated differences between human and canine blood in the hemoglobin-independent plot of log P_{CO_2} against pH. Those findings and our need to characterize the acid-base status of swine blood led to these investigations. As a result, acid-base curve and alignment nomograms were constructed for swine blood, and the methodology used for their construction was reappraised.

Collection and Handling of Blood

Four studies were performed; each study used the blood of a different pig. Each pig's blood was handled in a similar fashion. Pigs were anesthetized with thiopental, and 330 ml of arterial blood was collected in heparin (33 units/ml blood). Whole blood was centrifuged and three red blood cell dilutions (to packed cell volumes of approximately 9, 27, and 45%) were prepared from the separated red blood cells and plasma. A sample of well-mixed original whole blood and samples of each dilution were placed in ice for later determination of total protein (162), hemoglobin (162) 2,3-diphospoglycerate (163) and methemoglobin (164) concentration. Blood samples were prepared in duplicate at base excesses (BE) of -25, -20, -15, -10, -5, 0, +5, +15 and +20 mEq/l at each of the three hemoglobin concentrations (a total of 60 samples) by adding 100 µl of working acid or base solution (see below) to 3.9 ml of blood. To prevent red cell lysis, blood samples were briefly centrifuged at low speed, and the acid or base solution was added to the swirling supernatant plasma. Samples were then gently but thoroughly mixed. Blood preparation was followed by tonometry and measurement of pH. One member of each pair of blood samples was equilibrated for 7 min in an Instrumentation Laboratories Model 213 tonometer with a gas mixture of 2.72% CO_2 in O_2; the other member of the pair was similarly equilibrated with a gas mixture of 9.60% CO_2 in O_2. The gas mixtures had been previously analyzed in triplicate using the method of Scholander (165). (When these gas flows and concentrations and blood volumes were used in preliminary experiments, equilibration of blood with CO_2 was achieved within 4-5 min.)

We measured pH using a Severinghaus-UC electrode (122) thermostatically controlled at 38.8°C, and a Lorenz Model 3 DBM-3 amplifier. The pH electrode was calibrated with precision reference buffers (pH 6.839 and 7.379 at 38.8°C, Radiometer, 3-ml sealed glass ampules). Electrode calibration was checked with the 7.379 buffer before and after each blood sample reading. Measurements were performed in duplicate with a maximal allowable difference between the two determinations of 0.003 pH units. The mean (± SD) of the difference between the paired readings for all samples, calculated without respect to sign, was 0.001 ± 0.001 pH units. Measurements of pH were corrected for red cell suspension effect (166, 167). Carbon dioxide partial

pressure was measured in duplicate using a CO_2 electrode (Radiometer E5036) in a steel-and-glass cuvet (Radiometer D616) thermostatically controlled at 38.8°C. The electrode was calibrated with gas mixtures analyzed in triplicate using the method of Scholander (165). A reading of a standard gas with a P_{CO_2} close to that expected for the blood sample was taken before and after each blood sample reading. Blood CO_2 tensions were systematically measured to ensure equilibration of blood with CO_2. Mean (± SD) difference between measured and expected blood P_{CO_2} (calculated without regard to sign) was 0.88 ± 0.27 torr at P_{CO_2} of 67.9 torr. Readings for pH and P_{CO_2} were corrected for electrode drift.

Preparation and Standardization of Acid and Base Solutions

A 1.0 N solution of Na_2CO_3 (100%, certified alkalimetric standard, Fischer Scientific Co.) was prepared and used to standardize, by titration, what we determined to be a stock solution of 1.01 N HCl. The 1.01 N HCl was used as a titrant for a stock solution of what we determined to be 1.03 N $NaHCO_3$. Concentrations of 0.2 N, 0.4 N, 0.6 N and 0.8 N acid and base working solutions were prepared volumetrically from the stock solutions. All working solutions were titrated as described above. All titrations were repeated after completion of the bench laboratory work reported here; no differences were noted between determinations made before and after these experiments.

Data Analysis

The data generated for each pig resulted in three sets of values (one for each concentration of hemoglobin). Each set contained values for pH and P_{CO_2} for blood samples at each base excess (0 to 20 mEq/l of acid or base added). However, since the base excess of the blood drawn from the animal was not necessarily zero, the data were "normalized" to correct for any small acid-base imbalance at the time of sampling. To accomplish this, Siggaard-Andersen and Engel (168, 169) plotted constant CO_2 titration curves (pH vs. acid or base added) at both carbon dioxide tensions for each hemoglobin concentration. They curve-fit their data by eye and hand, and similarly shifted the axis for the added acid or base so that zero corresponded to pH 7.400 for the P_{CO_2} 40 torr curve (O. Siggard-Andersen, personal communication).

In following their methodology, we noticed that minor differences in curve-fitting and shifting the data "by eye" resulted in relatively large differences in the final nomograms. Unable to arbitrarily resolve these observed differences, we used precise mathematical and graphical techniques which were implemented by a computer.

For each concentration of hemoglobin, we calculated regression coefficients using a forward stepwise (with a backward glance) selection procedure (170) to fit the model:

$$pH = (C_1+C_2*BE+C_3*BE^2+C_4*BE^3+C_5*BE^4)*\log P_{CO_2}+$$

$$C_6+C_7*BE+C_8*BE^2+C_9BE^3+C_{10}*BE^4$$

This model has the following properties: a) for any given BE the relationship between pH and log P_{CO_2} is linear; b) the slope and intercept of this relationship may vary non-linearly with BE; and c) for each concentration of hemoglobin, the calculated coefficients define a model that fits the data with high statistical significance ($R^2 > 0.99$).

For each level of hemoglobin, the equation was "normalized" to a pH of 7.400 for a BE of zero and a P_{CO_2} of 40.0 torr, Orr et al. (171) in six awake chronically catheterized swine. These investigators measured Pa_{CO_2} as 38 torr and pH_a as 7.43 (BE less than 1 mmol/l). This seemed sufficiently close to the human standard of P_{CO_2} of 40 torr and pH of 7.40 to retain these values for BE = 0 for the purpose of nomogram construction. This "normalization" was accomplished by solving each derived regression for BE at pH = 7.4 and P_{CO_2} = 40 torr using the Jenkins-Traub three-stage algorithm (172). The result, BE_{error}, represented the deviation of the acid-base status of the animal from zero at the time the blood was drawn. Values for the amount of acid or base added (BE) were then adjusted (shifted) by the amount of BE_{error}. The above regression model was then refit using the shifted BE values.

Curve nomogram. Using the equations resulting from the above curve-fitting procedure, we calculated the relationship between pH and log P_{CO_2} for each of the three concentrations of hemoglobin at each level of BE. Siggaard-Andersen and Engel (169) stated that for each level of BE there exist a single pH and P_{CO_2} that are independent of hemoglobin concentration. Therefore, for each level of BE, the three lines calculated above should intersect at a single point. Brodda (173) has calculated that this can only occur if shifts in water between the red blood cell and plasma that result from changes in pH are taken into account. Experimentally, the three iso- hemoglobin lines at each level of BE result in three intersections. Several approaches are possible when approximating the hemoglobin-independent point by computer. For example, the three points of intersection could be averaged. However, this method can be shown to be subject to large error when two of the hemoglobin lines are nearly parallel. Other simple methods of approximation are similarly subject to error. At the expense of being more complex and cumbersome, our approach avoided this potential error.

We approximated the hemoglobin-independent point by calculating the point which minimized the mean square difference in pH and in log P_{CO_2} between the point and the three buffer slope (isohemoglobin) lines. Intuitively, such a point would be the point requiring the smallest change in the projection of the three hemoglobin lines in order to produce a common intersection. We derived this point in the following fashion.

Let $(pH_{ind}, \log P_{CO_{2_{ind}}})$ be the Hb-independent point.

Let m_i and b_i, $i = 1, 2, 3$ be the slopes and intercepts of the three linear relationships calculated from the regression model for a given BE (i.e., $pH = m_i \log P_{CO_2} + b_i$). Solve the following set of equations for pH_{ind} and $\log P_{CO_{2_{ind}}}$:

$$\frac{dX}{d(pH_{ind})} = 0$$

where $X = (pH_1 - pH_{ind})^2 + (pH_2 - pH_{ind})^2 + (pH_3 - pH_{ind})^2$

$$\frac{dY}{d(\log P_{CO_{2_{ind}}})} = 0$$

$$\text{where } Y = (\log P_{CO_2 1} - \log P_{CO_2 ind})^2 + (\log P_{CO_2 2} - \log P_{CO_2 ind})^2 +$$

$$pH_i = m_i \log P_{CO_2 ind} + b_i \qquad \text{for } i = 1,2,3$$

$$\log P_{CO_2 1} = \frac{pH_{ind} - b_i}{m_i}$$

A curve nomogram was then plotted by connecting the hemoglobin-independent points for a series of BE values.

Alignment nomogram. Curve-shifted data were used for a comput- erized construction of the alignment nomogram, in a manner similar to that described by Siggaard-Andersen (174).

"Mean" Pig

For each pig, the previously derived regression equations (one for each concentration of hemoglobin) were used to calculate pH values at each standard P_{CO_2}, at each standard base excess. The resulting four pH values (one per pig) at each P_{CO_2}, BE and concentration of hemoglobin were averaged, thus producing a set of data representing the "mean" pig. Raw data could not be used for this purpose because the base-excess values of the sampled blood differed slightly among pigs, thus requiring differing degrees of "curve- shifting" to achieve "normalization". "Mean" pig data were then handled as if they were from a single pig, and the above described analysis was performed. The result was separate "mean" curve and alignment nomograms.

3. Determination of anesthetic dose of ketamine or thiopental, in hypovolemic swine.

The need for this study was suggested following the presentation of data from study #1 to our departmental research seminar. Although the minimal anesthetic doses of ketamine and thiopental are well described in man and animals during normovolemia, the data do not exist for the hypovolemic state. If hypovolemia causes the minimal required doses of anesthetic agents to be altered differently among agents, results from study #1 would be difficult to interpret. We therefore conducted the following study to determine the minimal anesthetic doses of thiopental and ketamine in our hypovolemic model.

Eight swine (Chester-White-Yorkshire cross) littermates (mean weight $\pm$ SE), 15.3 $\pm$ 0.4 kg) were divided into four pairs on the basis of similarity in weight. One of each pair was randomly assigned to receive thiopental (group T) or ketamine (group K). All animals were in good health for each study.

Animals were anesthetized four times while normovolemic, at least two days separating each study. Unmedicated animals were placed in a sling, and a cannula was inserted into an ear vein. In random order, on four separate occasions, group K animals were given ketamine 12.5, 15, 17.5, or 20 mg/kg iv. Group T animals were given thiopental 7.5, 10, 12.5, or 15 mg/kg iv. Eventually, each animal received all four doses.

Animals were anesthetized four times while hypovolemic, one week separating each study. Unmedicated animals were anesthetized briefly with halothane in oxygen and nitrogen while arterial and venous cannulae were inserted. Arterial blood samples were obtained; and PO_2, PCO_2, and pH measured by appropriate electrodes. Arterial blood pressure was transduced (Statham Model 23Db) and recorded (Gould Model 2800 polygraph). Halothane was discontinued, the animal allowed to awaken, and placed in a sling. Further experimentation was delayed until the end-tidal partial pressure of halothane, as measured by mass spectroscopy, fell to less than 0.5 torr (0.05 MAC). To prevent hypoxia during and after blood loss, animals were given 1-2 l/min oxygen by mask. Each animal was bled by 30% of its estimated blood volume (106) over a 30-min period. To ensure stability, 30 min of observation followed. In random order, on four successive weeks, group K animals received one of four IV doses of ketamine: 2.5, 5, 7.5, or 10 mg/kg IV; group T animals received thiopental, 5, 7.5, 10, or 12.5 mg/kg IV. Eventually each animal again received all four doses.

Following the administration of each drug in either the normovolemic or hypovolemic state, the animal's response (i.e., movement or lack of movement) to a clamp on the tail was determined. Tail-clamp tests were performed 10, 20, 30, 45, 60, 90, 120, 180, 240, and 300 sec. after drug administration.

The data obtained will be useful in evaluating the data from study #1. In addition, the data will be useful to the practicing anesthetist, who must administer these drugs to a hypovolemic soldier. These results will allow us to provide recommendations to USAMRDC regarding the dose of these anesthetic agents for use for induction of anesthesia in a wounded soldier who is hypovolemic, and whose blood volume cannot be adequately restored prior to surgery.

Statistical Treatment of Data: Responses to clamp on the tail were analyzed statistically using the method of Waud (131). In addition, the

maximum dose of drug which failed to prevent movement in each individual animal and the minimum dose of drug which prevented the animal from moving was averaged for each animal. This average for the four animals in each group were compared between normovolemic and hypovolemic states by using student's t-test. Differences between the two states were compared for the two drugs, using student's t-test.

4. Determination of minimal alveolar anesthetic concentration (MAC) of halothane and nitrous oxide, in swine

In order to perform study #5 described below (comparison of cardiovascular sequelae of induction of anesthesia with nitrous oxide or halothane, in swine) it was first necessary to carefully determine equivalent anesthetic concentration of these agents in our animal model. Although MAC has been determined for man and many laboratory animals for both nitrous oxide and halothane (132), it has not been previously determined in swine. MAC for the same anesthetic agent differs to a fair extent among species (132) and assumption of an average concentration for use in study 5 could create errors sufficiently large to invalidate the study. We, therefore, determined MAC for nitrous oxide and halothane in swine.

Eight young, healthy swine (weight 24.7 $\pm$ 1.1 kg, mean $\pm$ S.E.; age approximately 10 weeks) were anesthetized, in random order, with either halothane in 30% oxygen, balance nitrogen, or with halothane, 70% nitrous oxide and 30% oxygen. The trachea was intubated, and the animal allowed to breathe spontaneously while in the lateral decubitus position. Partial pressures of oxygen, carbon dioxide, nitrous oxide, and halothane were measured continously by mass spectrocopy (Perkin-Elmer model MGA1100AB) at the endotracheal tube orifice. Rectal temperature was measured with a thermister (Yellow Springs) and MAC determined, as described below. The anesthetic was then changed by either the addition or elimination of nitrcus oxide, and MAC determined again. When nitrous oxide was eliminated, we waited until its end-tidal partial pressure fell to less than 0.23 torr before continuing experimentation.

MAC was determined in a manner similar to that described by Eger and Saidman (133). Briefly, following each change in anesthetic concentration, end-tidal partial pressure was held constant for a minimum of 15 minutes. A clamp was placed on the tail of the animal. The animal's response (movement or no movement) to the stimulus was noted. If the animal moved, anesthetic concentration was increased by approximately 5-10% of its concentraton. If the animal did not move, anesthetic concentration was decreased by a similar amount. When a concentration was eventually reached for which the animal's response changed, changes in anesthetic concentration were diminished so that the concentration of halothane at which the animal moved did not differ by more than 0.05% halothane from the concentration at which the animal did not move.

When N_2O was used, its end-tidal concentration was held constant at 70% (70.14 $\pm$ 0.05%, mean $\pm$ S.E.). The MAC for N_2O was determined by difference, in each animal, and the results averaged. To determine the individual MAC for N_2O, the concentration of N_2O was multiplied by the inverse of the fraction of a MAC for halothane which the N_2O contributed for each animal:

$$M_N = (C_N) \frac{M_H}{M_H - M_{H+N}}$$

where M_N is the MAC for nitrous oxide, in %; M_H is the MAC for halothane, in %; M_{H+N} is the MAC for halothane, in %, in the presence of nitrous oxide at a concentration of C_N. In this manner, MAC was determined for each animal, and the results averaged.

The mass spectrometer was calibrated with calibrated tanks of halothane and nitrous oxide. We produced the halothane standard tank, and calibrated it multiple times against standards made by vaporizing a measured volume of halothane in a sealed flask of known volume. The calibration tank of N_2O was commercially produced and calibrated (Liquid Carbonics); we further checked it against the mass spectrometer calibrated with 100% N_2O.

Data from this study will allow us to use the appropriate concentration of anesthetic agent for study 5.

5. Evaluation of nitrous oxide for induction of anesthesia during hypovolemia.

The purpose of this experiment is to test the hypothesis that nitrous oxide does not offer any cardiovascular or metabolic advantage over other anesthetic agents when used for induction of anesthesia during hypovolemia.

Because the data from study #4 showed the minimal alveolar anesthetic concentration of nitrous oxide to be close to 260%, the depth of anesthesia in those animals given nitrous oxide in study #1, was not comparable with that of other groups. Therefore, the following experiment will be performed. The approach is the same as for study #1 described in this report (pages 15-17), except for the groups of anesthetic agents:

Group I: Nitrous oxide, 70%
Group II: Halothane, 0.31%

these concentrations of anesthetic agents are equivalent, i.e. 25% MAC.

The data from this experiment will show the comparative cardiovascular influence of nitrous oxide with halothane when used for induction of anesthesia during significant hypovolemia. These results will allow us to provide recommendations to USAMRDC regarding choice of anesthetic agents for induction of anesthesia in a wounded soldier who is hypovolemic, and whose blood volume cannot be adequately restored prior to surgery. Should nitrous oxide not prove to have any advantage over other anesthetic agents, it will further allow us to recommend that USAMRDC recommend to the appropriate agency that it consider the cessation of supplying nitrous oxide to battlefield facilities, (supplying N_2O to battlefield facilities represents a large logistical burden).

6. Importance of the renin-angiotensin system during hypovolemia.

As we began our pilot studies to examine the interaction of anesthetic agents, carbon dioxide, and the renin-angiotensin system with hemorrhage, it became clear to us that the animals were not behaving in a way which one might expect from the published literature. We therefore designed and conducted the following study to test for the importance of the renin-angiotensin system during hemorrhage.

Ten swine were studied. They were briefly anesthetized and prepared as described for study #1 in this report (pages 15-17). Following elimination of all anesthetic agent, variables as outlined for study one of this report were measured and calculated. These measurements and calculations were repeated after a single intravenous dose of angiotensin II (100 nanograms per kilogram). Saralysin was then continuosuly infused (2 micrograms per kilogram per minute) for 10 minutes and measurements and calculations repeated, with the infusion continuing. With the saralasin infusion continuing, response to a second dose of angiotensin II (100 nanograms per kilogram) was examined and measurements and calculations repeated. In this manner we were able to test the normovolemic response to angiotensin II, and to saralasin; and to demonstrate the effectiveness of saralasin blockade of angiotensin II effects.

Thirty minutes after discontinuation of the saralasin infusion, and demonstration of return to normal values, animals were bled by 30% of their blood volume as described for study #1 of this report (pages 15-17) and measurements and calculations performed. Animals were then again given the same single intravenous injection of angiotensin II (100 nanograms per kilogram) to demonstrate the effects of angiotensin II during hemorrhage. The animals were then randomized into two groups:

Group one: saline infusion

Group two: saralasin infusion

Group one animals were then infused with saline (same fluid volume rate as group two animals) for a period of ten minutes. Group two animals were infused for the same period of time with saralasin (2 micrograms per kilogram per mintue). Measurements and calculations were repeated. Demonstration of blockade of effects of angiotensin II, or of lack thereof, was accomplished with another injection of angiotensin II (100 nanograms per kilogram).

Statistical treatment of data: Changes in systemic vascular resistance were compared for each injection of drug by paried t-test, and for the same state between groups one and two by unpaired t-test.

The data from this set of experiments will allow us to quantitate the importance of the renin-angiotensin system during hemorrhage in swine. This data is essential for investigations into the mechanisms of action of how anesthetic agents cause deterioration of an animal's compensation for hemorrhage.

C. Results:

1.. Awake Hemorrhage:

We have successfully established the awake hemorrhagic swine model in our laboratory. Loss of 30% of estimated blood volume results in physiologic sequelae similar to those occurring in other laboratory animals and man. See table 1, page 66. Thirty percent hemorrhage causes decreased right-and left-sided filling pressures (right atrial and pulmonary arterial wedge pressures), resulting in a 38% decrease in cardiac output. Despite a 3 fold-increase in plasma renin activity and a doubling of plasma catecholamine concentration, resulting in increased systemic and pulmonary vascular resistances, compensation was inadequate. Mean arterial blood pressure fell 24%, and mean pulmonary arterial pressure, 29%. Total-body oxygen consumption increased systemic and hypoperfusion was evident from increased blood lactate concentration and base-deficit (decreased base-excess).

2. Comparison of Ketamine, Thiopental, Enflurane, Halothane, Nitrous Oxide and Isoflurane During Induction of Anesthedsia During Moderate Hypovolemia: The experimentation; biochemical, enzymatic, and hormonal assays; and data analyses have been completed. These are being reported in an abstract (134) and two manuscripts (see addendum b5, and appendices 1 and 2).

a. Induction of anesthesia with ketamine or thiopental (see table 2, pages 67-68).

Control Animals: After the initial changes caused by hemorrhage, no variable further changed in control animals during the hypovolemic period.
Five Minutes after Induction: Five minutes after administration of ketamine ($P < 0.05$), but not thiopental ($P > 0.05$), plasma epinephrine, norepinephrine, and renin activity had increased. Despite these differences in circulating vasoactive agents, ketamine and thiopental produced similar changes in compensatory cardiovascular responses to hemorrhage. Systemic vascular resistance was less in Groups K and T than in Group C. Neither agent changed right- or left-sided cardiac filling pressures. Although ketamine and thiopental significantly decreased heart rate, the resulting rates did not differ significantly from the rate for Group C. Although only ketamine decreased stroke volume (0.95 ± 0.12 to 0.70 ± 0.10 ml/kg, $P<0.005$), the resulting values did not differ among groups. Cardiac output decreased similarly in Groups K and T to values less than that for Group C. As a result, mean systemic blood pressures did not differ between Groups K and T; however, both groups had pressures that were less than those for Group C. Oxygen consumption did not differ among the groups, but whole-blood lactate concentrations increased similarly in Groups K and T.

Thirty Minutes after Induction: Thirty minutes after induction, most values had recovered towards preanesthetic levels during hypovolemia; however, significant differences remained. Plasma epinephrine concentration was still greater in Group K than in Groups C and T (which were not different from each other). Although plasma norepinephrine concentration was greater in Group K than in Group T, these two groups did not differ from Group C. Plasma renin activity was greater in Group K than in Group T, but the activity in these groups was not different from Group C. For Groups K and T, SVR did not differ from each other, but was less than that for Group C.

Right- and left-sided cardiac filling pressures and heart rate remained similar, and cardiac output no longer differed among groups. Also, the resultant mean systemic arterial pressure was similar for Groups T and K; both were less than that for Group C.

Oxygen consumption did not differ among groups, but whole-blood lactate concentration continued to increase and base-excess continued to decrease significantly only in Group K ($P < 0.05$).

Return of Shed Blood: Thirty minutes after return of shed blood, cardiac output was greater in Group K than in Groups C or T. Blood lactate was still greater in Group K than in either Group T or C. There were no other significant differences among groups.

Ninety minutes after return of shed blood, there were no signiticant differences among groups for any variable.

All animals survived 24 hours, at which time they were killed.

b. Induction of anesthesia with enflurane, halothane, and isoflurane (see Table 3, p. 69).

There were no differences among the four groups in the normovolemic or in the hypovolemic condition. Hemorrhage caused the expected cardiovascular and metabolic effects. Right- and left-sided cardiac filling pressures decreased and although plasma renin activity, plasma concentrations of norepinephrine and epinephrine, heart rate, and systemic vascular resistance increased, stroke volume, cardiac output, and systemic arterial blood pressure decreased. In addition, base-excess decreased and whole-blood lactate concentration increased. Hematocrit decreased from 36% to 31%.

Halothane, enflurane, and isoflurane caused similar cardiovascular and metabolic effects when given to induce anesthesia during hypovolemia; all were different from control animals whose values remained unchanged during the comparable time period (see table 3, page 69). Induction of anesthesia caused a significant reduction in cardiac output and systemic vascular resistance, thus causing a profound decrease in mean systemic blood pressure. Administration of all anesthetics resulted in increased blood lactate. Oxygen consumption did not change. Plasma renin activity increased but plasma catecholamines did not change. Thirty minutes after induction of anesthesia (anesthetic held constant at the above concentrations) cardiac output had increased, therefore causing an increase in mean systemic blood pressure; systemic vascular resistance, cardiac filling pressures, and heart rate did not change appreciably.

3. Swine blood acid-base chemistry:

The mean acid-base curve nomogram for swine blood is depicted in Fig. 5, p. 71; the data are presented in Table 4, p. 70. We compared our curve nomogram for swine blood with that of Siggaard-Andersen (168) for human blood, and with that of Scott Emuakpor (161) for canine blood (Fig. 6, p. 72). nomogram is shown in Fig. 7, p. 73.

4. Determination of anesthetic dose of ketamine or thiopental, in hypovolemic swine.

This study has been completed, and a manuscript prepared (see appendix).

Hypovolemia in swine reduced the minimum anesthetic dose for both thiopental ($P < 0.025$) and ketamine ($P < 0.01$); (see table 8, page 74). These reductions (thiopental 33% $\pm$ 5%; ketamine, 40% $\pm$ 5%) were not statistically different ($P > 0.2$) from each other. After hemorrhage and before drug administration, mean ($\pm$ SE) arterial blood gas values were as follows: PO_2, 177.8 $\pm$ 20.1 torr; PCO_2, 41.9 $\pm$ 1.5 torr; and pH, 7.323 $\pm$ 0.11. Mean ($\pm$ SE) arterial blood pressure was 92 $\pm$ 3 torr after hemorrhage, 69 $\pm$ 9 torr after administration of ketamine, and 66 $\pm$ 7 torr after administration of thiopental.

5. Determination of minimal alveolar anesthetic concentration (MAC) of halothane and nitrous oxide in swine.

This study has been completed and a manuscript prepared (see appendix).

MAC for halothane in normovolemic swine was determined to be 1.25 $\pm$ 0.04% (mean $\pm$ S.E.; range: 1.08 - 1.47%). MAC for N_2O was determined to be 277 $\pm$ 18% (mean $\pm$ S.E.; range: 204 - 361%).

Temperature of the animals was 37.7 $\pm$ 0.2°C; hematocrit was 35 $\pm$ 0.7%.

6. Evaluation of nitrous oxide for induction of anesthesia during hypovolemia.

The experimentation for this study has been completed. Biochemical and enzymatic assays are not yet complete. Data reduction and analyses are proceeding.

Thirty percent blood loss decreased right- and left-sided cardiac filling pressures, mean systemic blood pressure, stroke volume, and cardiac output. Systemic vascular resistance, oxygen consumption, blood lactate concentration and plasma cathecolamines increased (see table 9). These changes are similar to those observed in a larger group of swine (see table 1). Before induction of anesthesia, there were no differences between the two groups. Five minutes after induction of anesthesia (see table 10) although group two animals had higher plasma norepinephrine concentrations, the only other significant difference was the higher heart rate for group two. Thirty minutes after induction of anesthesia (see table 11), nitrous oxide administration associated with higher arterial blood pressure, heart rate, systemic vascular resistance, and oxygen consumption, but lower stroke volume; there were no differences between groups for cardiac output or blood lactate concentrations. After return of shed blood, plasma cathecol concentrations were higher in group two; there were no other significant differences. After elimination of the anesthetic agents, there were no differences between the groups.

7. Importance of the renin-angiotension system during hypovolemia.

The experimentation for this study has been recently completed. Biochemical and enzymatic assays are not yet complete. Data reduction and analyses are proceeding.

During normovolemia, the swine behaved as expected in response to injection of angiotensin II: a significant increase in systemic vascular resistance (see figure 13). Saralasin infusion during normovolemia had no effect on systemic vascular resistance, but completely blocked the effects of injection of angiotensin II (see figure 13). In response to hemorrhage, systemic vascular resistance increased significantly (see figure 14). There were no differences between the two groups in their response to angiotensin II, saralasin, or saralasin plus angiotensin II during normovolemia. Similarly, there was no difference between groups in their response to hemorrhage. Similarly, both groups had similar increase in systemic vascular resistance in response to angiotensin II when injected following hemorrhage (see figure 15). During hypovolemia neither infusion of saline, nor infusion of saralasin altered systemic vascular resistance. In response to these infusions, the groups also failed to show any differences in mean systemic arterial blood pressure, heart rate, cardiac output, right atrial pressure, or blood lactate concentration (see table 12). Saline did not block effects of angiotensin II during hemorrhage, however infusion of saralasin completely blocked the effects of angiotensin II (groups significantly different, $P < 0.05$). Following termination of infusion of either saline or saralasin, both groups again behaved similarly in response to angiotensin II (see figure 15).

D. Discussion:

1. Hemorrhage model:

The swine is an excellent animal for laboratory investigations involving hemorrhage. Swine are more readily available than dogs, and in more uniform size. Their cardiovascular physiology more closely resembles that of man than does the dog.

Our supplier (J.G. Boswell Co.) artificially inseminates all swine, thus breeding is exactly controlled, and genetic make-up known and reproducible. Their response (cardiovascular, metabolic, hormonal) to hemorrhage is entirely in keeping with what is known from other laboratory animals and man. Of passing note, we were not able to substantiate the claim of others (106) that the swine has high pulmonary artery pressure.

Our animals are undoubtedly not "at rest" as are those of Hannon (104-105). However, it is necessary to ventilate the awake normovolemic animals in order to conduct valid comparison of that state with the state following induction of anesthesia. Nevertheless, the awake normovolemic values for our swine appear to fall within the broad range of values reported by others for unanesthetized swine (104-110, 130). Hannon (104) has discussed the possible reasons for data variability in the literature, and those need not be repeated here.

2. Comparison of ketamine, thiopental, enflurane, halothane, and isoflurane for induction of anesthesia during moderate hypovolemia.

a. Ketamine and thiopental.

The cardiovascular effects produced by induction of anesthesia with ketamine during hypovolemia differ from those seen during normovolemia. Heart rate, mean systemic blood pressure, and cardiac output increase when ketamine is administered to normovolemic animals[63,66,67,77] or man[54,55,67,70]. In contrast, these variables decrease during hypovolemia. In our study ketamine and thiopental produced identical cardiovascular changes initially. Although these two anesthetics affected plasma catecholamine concentrations and renin activity differently, both caused similar deterioration of the animal's compensation for hemorrhage, and decreased SVR, cardiac output, and BPa. Thirty minutes after induction, hypovolemic animals who had received ketamine for induction became progressively more acidotic, while those who had received thiopental or no anesthetic did not. Administration of ketamine further increased circulating catecholamine concentrations above the already elevated levels caused by the sympathetic response to hypovolemia. Thus, one portion of our hypothesis was not supported. In swine, the sympathetic response to 30% hemorrhage was not maximal; further sympathetic response was possible. The concomitant increase in plasma renin activity after administration of ketamine may be a function of increased sympathetic activity,[89,136,137] other circulating substances,[89] or a separate action of ketamine. The progressive lactic acidosis 30 min after induction, seen only in the ketamine group, may be a result of increased oxygen demand caused by increased sympathetic activity without concomitantly increased blood flow, or decreased hepatic uptake of lactate, or both.

In intact experimental animals, it is not certain which measure best reflects inadequacy of tissue perfusion. Huckabee proposed blood "excess lactate" as a measure[138], but later Cain demonstrated blood lactate concentration to be at least as good[139], if not a better measure[140] of oxygen deficit. Previously, we have shown in asplenic dogs, bled while anesthetized, that blood lactate concentration and base-deficit developed to a greater extent when they were anesthetized with ketamine than with halothane, enflurane, or isoflurane[82]. Conversely, Longnecker et al. have reported higher excess lactate in rats bled while anesthetized with halothane than similar rats anesthetized with ketamine[141]. However, we have calculated that those rats anesthetized with ketamine had a greater base-deficit (approximately 11 mmol/l) than those anesthetized with halothane (approximately 2.5 mmol/l). Recently, Longnecker et al.[142] reported higher PO_2 in cremaster muscle of rats bled while anesthetized with ketamine than in rats bled while anesthetized with halothane. However, since arterial blood gases were not measured, and all animals breathed room air spontaneously, it is not possible to determine whether the tissue Po_2 differences were related to perfusion or arterial oxygen tension, or both. Furthermore, since compensatory events in response to hemorrhage differ among tissues, these measurements do not necessarily reflect conditions in other organs.

In these experiments, despite the increase in catecholamine concentrations and renin activity, SVR, BPa, and cardiac output decreased. This failure of massively increased levels of circulating catecholamines to maintain BPa, SVR, and cardiac output implies that ketamine has a powerful

opposing depressant effect, or that the maximal response to stimulation had been achieved. Ketamine has been shown to be a direct myocardial depressant,[65,66,143,144] not to cause contraction of rabbit aortic strips,[146] and to relax phenylephrine-induced contracted rabbit aortic strips[146]. Similarly, thiopental depresses the myocardium[52] and peripheral vasculature.[51] In our experiments, both anesthetics decreased SVR. The fall in stroke volume index at a time when left ventricular preload increased, seen after administration of ketamine, tends to indicate myocardial depression. However, since heart rate, afterload, and myocardial compliance were not controlled, no conclusion can be drawn. Alternatively, the increase in circulating catecholamines in the animals given ketamine could have been a response to the hypotension produced by the drug. This would imply that thiopental blocked a similar response. Our experimental data can not differentiate between these proposed mechanisms. Nevertheless, our data do support the second part of our hypothesis: that further sympathetic stimulation during induction of anesthesia during hypovolemia is not beneficial. Several aspects of our methodology should be discussed. Our animals were not "trained"; therefore, data obtained in the absence of anesthesia, with the animals' tracheas intubated and the animals mechanically ventilated, may not be equivalent to data for "resting" animals. Nevertheless, cardiovascular data we obtained for the unmedicated, normovolemic state fall within the range of values reported by other investigators.[106-109,111,113-115] Furthermore, hypovolemic and/or traumatized humans are not in a "resting" state. The few limited reports of hemorrhage in unmedicated swine have shown an arterial blood pressure response similar to that of our animals.[105,109,111] Because detailed cardiovascular response of unmedicated swine to hemorrhage has not been reported, we cannot compare some of our results with those of other investigators. Hemorrhage produced changes similar to those we have observed in a larger group of similar swine (table 1, p 66). All cardiovascular and metabolic responses to hemorrhage in our swine are consistent with what is known for man. Although the dog has been the species most frequently used to study hemorrhage, its response and that of the rat differ in important ways from that of man.[148,149] In these species, contraction of the hepatic sphincter causes splanchnic engorgement and a number of sequelae not seen in man.[148,149] The response of the gastrointestinal tract of swine in shock resembles that of man.[55] Because we did not conduct a dose-response study, we cannot address the question of whether other doses of ketamine or thiopental could have produced different effects during hypovolemia. However, the minimal anesthetic dose required during normovolemia was determined for both agents and individually for each animal. This dose was then reduced in accordance with our findings that hypovolemia similarly reduces the anesthetic requirement for thiopental and ketamine. Smaller doses would not have been anesthetic, and other cardiovascular responses could have occurred. Our data do not demonstrate a beneficial effect from using ketamine during hypovolemia. Studies reporting satisfactory use of ketamine for patients in "hemorrhagic shock" have had some shortcomings: the concomitant use of other drugs; and/or the failure to substantiate major blood volume deficit, to indicate the dose of ketamine administered, or to document cardiovascular responses at specific time intervals.[53,78,79] The literature concerning the use of thiopental for induction of anesthesia during hypovolemia is also anecdotal. In World War II, the drug was used in doses of at least 500 to 1,000 mg. Patients breathed spontaneously; and in many cases, inspired oxygen concentration was 21%. It is not surprising that the result

was sometimes catastrophic. Ketamine was introduced 30 years later, after use of controlled ventilation and high inspired concentrations of oxygen had become routine, and after anesthesiologists had become more skilled at recognizing and treating hypovolemia. These improvements alone would have improved outcome. If anesthesia must be induced in a hypovolemic patient, ketamine 0.5 mg/kg iv is often administered. Sometimes the result is satisfactory; sometimes severe cardiovascular depression results. Because many other events occur almost simultaneously (endotracheal intubation, positive-pressure ventilation, skin incision and rapid initiation of surgery, continued fluid infusion), the outcome does not reflect the effects of the anesthetic agent alone. Our data indicate that moderate hypovolemia does not produce a maximal increase in circulating catecholamines. Administration of ketamine, but not thiopental, causes a further increase. However, the increased plasma concentrations do not further stimulate the circulation, either because they are above the maximal possible effective concentrations, or because their effect is overwhelmed by the depressant qualities of ketamine, or both. Administering ketamine for induction of anesthesia during hypovolemia did not offer any advantages over thiopental when both were used at the minimal anesthetic dose. The clinician should note that an anesthetic agent is not a substitute for adequate restoration of blood volume and venous return; and when an anesthetic must be administered during significant hypovolemia, cardiovascular depression should be expected.

b. Enflurane, halothane, and isoflurane. A desirable property of any anesthetic agent used in the presence of hypovolemia would be to have minimal effect on the compensatory mechanisms for hemorrhage. During normovolemia, in healthy volunteers, halothane tends to maintain systemic vascular resistance (5,6) and isoflurane tends to maintain cardiac output (14,15). Therefore, one might have thought that these agents could be used preferentially in the presence of hypovolemia. We have found that halothane, enflurane, and isoflurane cause similar detrioration of cardiovascular compensation for hemorrhage when used to induce anesthesia during hypovolemia. The administration of even a reduced dose of these anesthetics (0.4 MAC) caused a profound decrease in cardiac output, systemic vascular resistance, and therefore, mean systemic blood pressure. The decrease in stroke volume, without a change in heart rate or filling pressures implies myocardial depression, although afterload and myocardial compliance were not controlled. In addition, the anesthetics prevented a reflex increase in heart rate and an increase in plasma catecholamines.

Although, the greatest blood lactate concentrations were seen with enflurane, implying the greatest mismatching of oxygen supply and demand, the magnitude of the lactate concentrations implies a reduction in oxygen demand caused by all three agents. Similarly, we have found that halothane and isoflurane, but not enflurane, reduced oxygen demand more than supply in dogs bled during halothane, enflurane, or isoflurane anesthesia (82).

3. Swine blood acid-base chemistry.

Our mean curve and alignment nomograms for swine blood are different from nomograms for human blood (168,174) and canine blood (161) (Fig. 6). As a technical check, we performed similar but limited experiments with blood of two human volunteers. The resultant limited nomograms (30 data points, at hemoglobin concentrations of 3, 10, and 15 g/dl) were similar to that of Siggaard-Andersen (174) between base excess of -10 and +10 mmol/l ($P>0.5$), but different from our swine nomogram ($P<0.001$). To compare the swine alignment nomogram with that drawn by Siggaard-Andersen for human blood (174), we plotted our data of known pH, P_{CO_2}, hemoglobin concentration and base excess on the Siggaard-Andersen alignment nomogram as if we were unaware of the true base-excess value. The base-excess values determined from the Siggaard-Andersen nomogram were compared with the true BE values. The resultant estimated base excesses differed ($P<0.001$) from the known base excess of all blood samples at all concentrations of hemoglobin and base excess, except at a BE of zero, for which the results are definitionally identical. In nearly all cases, however, the calculated value was within $\pm$ 10% of the true value.

There are several possible explanations for the differences between our nomogram and that of Siggaard-Andersen. Neither set of data is based on the blood of a large population: Siggaard-Andersen used the blood of four people, we used four swine. However, in our experiments, individual variation did not appear to be an important problem.

Some of the observed differences may relate to differences in species. Scott Emuakpor *et al.* (161) described a curve nomogram for canine blood which differed from Siggaard-Andersen's curve nomogram for human blood. The buffer value of plasma proteins and hemoglobin can vary among mammalian species (175,176), and this may account for some, but not all (177), of the differences among the nomograms. Measured total protein of our swine blood (7.2 $\pm$ 0.3 g/dl) was similar to the normal value for man.

To create blood samples of altered base excess, we avoided important dilution of plasma proteins by adding small amounts of relatively concentrated (0.2-0.8 N) acid or base. We thereby produced some alterations in ionic strength of blood, which may account for some of the differences between our nomograms for swine blood and those of Siggaard-Andersen for human blood (168, 174). However, our curve nomogram for swine blood differs even more from the original curve nomogram of Siggaard-Andersen and Engel for human blood (169), for which the identical method of addition of acid or base was used.

To construct the nomograms, we followed the general methodology of Siggaard-Andersen. However, the two methodologies differ in several important ways.

We used a method different from that of Siggaard-Andersen to "shift" the original data in order to "normalize" the drawn blood to the established definition of BE = 0, pH 7.400, P_{CO_2} 40.0 torr. Siggaard-Andersen accomplished the following tasks graphically, fitting the curve and selecting the points by eye (18): a) curve-fitting the two constant CO_2 titration curve plots (pH *vs.* acid or base added) at each concentration of Hb; b) estimating similar data for P_{CO_2} 40 torr, assuming a linear relationship between log P_{CO_2} and pH, followed by curve-fitting of the P_{CO_2} 40 torr data as in a); c) estimating the axis shift (acid or base added) to align the P_{CO_2} 40 torr data

so that at a pH of 7.400, base excess was set equal to zero; d) estimating from the hand-drawn iso-P_{CO_2} curves, the pH at pre-selected levels of base excess. An example of this graphic process, using data from one of our swine, is shown in Fig. 4. We accomplished all of the above with a computer, the resulting curve-fit equations describing the data with an accuracy of more than 99.95%.

To draw the base excess grid, Siggaard-Andersen used his previously developed pH-log P_{CO_2} curve nomogram for one set of blood pH and P_{CO_2} values, and an empirical relationship between buffer base, hemoglobin concentration and base excess to estimate the required second pair of blood pH and P_{CO_2} values. Because of our uncertainties regarding the specificity of the pH-log P_{CO_2} curve nomogram and the empirical relationship described above, we chose to use our original data and the computer-generated curve-fits to that data to determine the base-excess grid.

To generate the continuous isohemoglobin lines of the base-excess grid from the original data, we developed computerized empirical mathematical equations that were plotted by computer. Siggaard-Andersen used points determined graphically to draw curves by hand. Although we have not examined systematically the differences between the two techniques, we did note before completion of the computer programs that seemingly small, unimportant interpretive differences that occurred when drawing curves by hand through the original data created relatively large differences in the estimated amount required to shift the "acid-or-base-added" axis. These differences created relatively large differences in the alignment nomogram.

Another difference between Siggaard-Andersen's nomogram and our own is the temperature at which tonometry and measurement of pH were performed. Siggaard-Andersen's experiments were performed at 38°C; ours were performed at 38.8°C (normal body temperature for swine). Siggaard-Andersen correctly stated that measurements performed at temperatures within $\pm$ 2°C of 38°C (the standard temperature of his nomogram) are "without any practically significant error" (21). We temperature-corrected some of our pH and P_{CO_2} data from 38.8°C to 38.0°C, and then estimated base excess from our nomogram. All estimates were within $\pm$ 0.1 mmol/l of the true value. Similarly, using established data for pK' solubility of CO_2 in plasma (178), we determined that change in calculated plasma HCO_3^- between 38.0°C and 38.8°C was less than 0.1 mmol/l.

Finally, there are differences in the methodology of measuring pH, the major variable upon which these nomograms rest. As a result of advances in design and construction of pH electrode (122) and amplifier (179), our determinations of pH probably had less variability (0.001 $\pm$ 0.001 pH units, SD) than did the measurements of Siggaard-Andersen. Variations in the measurement of pH that are usually considered minor (e.g., 0.003 pH units) result in surprisingly large differences in the final nomogram, because relatively small changes in the slope of nearly parallel lines greatly alters their point of intersection. Small variations in pH create the largest changes in the nomogram in the base-excess range of +10 to +25 mEq/l: the range in which our nomogram differs most from that of Siggaard-Andersen.

4. Determination of anesthetic dose of ketamine or thiopental, in hypovolemic swine.

Moderate hemorrhage (30% blood loss) produced similar reductions in the anesthetic requirement of these two different intravenous anesthetic agents.

Many variables affect the amount of drug required to produce anesthesia.[151] We were not able to study all, or even most, of these variables because of limitations imposed by our experimental design, which was selected to give the best answer to the question posed (does hypovolemia reduce anesthetic requirement for induction agents, and if so, does the reduction differ for different drugs?) Consequently, we have limited physiological information from these animals to complement the finding of reduced anesthetic requirement.

We do have, however, a good deal of information about other swine whose blood volume were similarly reduced (see table 1, page XX). Variables in these animals were measured during normovolemia and after 30% blood loss. Mean values ($\pm$ SE) decreased for arterial blood pressure (from 130 $\pm$ 2 torr to 98 $\pm$ 3 torr) for cardiac output (from 174 $\pm$ 5 ml/min/kg to 113 $\pm$ 6 ml/min/kg), and for base-excess (from 5.3 $\pm$ 0.3 mmol/l to 3.1 $\pm$ 0.3 mmol/l); and increased for blood lactate concentration (from 1.1 $\pm$ 0.1 mmol/l to 1.8 $\pm$ 0.1 mmol/l). When half of the drug dose which produced anesthesia during normovolemia was administered to these animals during hypovolemia, further reductions occurred in cardiac output (to 76.9 $\pm$ 5.1 ml/min/kg after ketamine, and to 74.0 $\pm$ 5.9 ml/min/kg after thiopental), and in mean arterial blood pressure (to 41.4 $\pm$ 3.5 torr after ketamine, and to 52.1 $\pm$ 7.8 torr after thiopental), and in base-excess. Blood lactate concentration increased even further. These mean arterial blood pressures are just below the level at which autoregulation is able to maintain normal cerebral blood flow. Thus, some of the decreased anesthetic requirement seen in these animals could have been a result of decreased cerebral blood flow. However, the animals in the present study had lesser decreases in blood pressure. Nor did they exhibit sufficient acidosis, hypercarbia, or decreased calculated oxygen content to account for a reduction of anesthetic requirement during hypovolemia.

We did not measure cerebral blood flow, and thus, cannot relate it to anesthetic requirement of these agents. However, since specific anesthetic site(s) of action are not known, knowledge of global cerebral blood flow would be of limited value. Knowledge of regional or microregional (if we knew which microregion) blood flow would be more helpful. Cullen and Eger related decrease in MAC to decreased oxygen delivery to the brain, either from decreased PaO_2[152] or severe isovolemic anemia[153]. A decrease in MAC correlates well with the occurrence of central acidosis[153]. Tanifuji and Eger found a 20% decrease in MAC for halothane in dogs made hypotensive to an arterial blood pressure of 40-50 torr by a combination of trimethaphan infusion, head-up tilt, and mild hemorrhage (approximately 12% blood loss)[154]. Rao et al[155] noted a decreased MAC for halothane in dogs made hypotensive by administration of pentolinium, trimethaphan, or nitroprusside, but stated that they did not find a correlation between decreased MAC and decreased carotid blood flow. In their experiments, mean arterial blood pressure did not fall below 60 mmHg, a level above that which autoregulation can no longer maintain cerebral blood flow. MAC however, decreased during the administration of all three drugs; carotid blood flow did decrease significantly in the dogs given two of the

drugs, but the large variability prevented achievement of statistical significance for those in the third group. Furthermore, in the dog, carotid blood flow is not a good indication of total cerebral blood flow. Thus, the literature does not contain a definitive study relating anesthetic requirement to cerebral blood flow.

Hemorrhage increases sympathetic activity[80] and circulating catecholamines in swine (see table 1, page 66). Since an increase in sympathetic activity increases anesthetic requirement, it is possible that anesthetic requirement would be reduced further when the sympathetic response to hemorrhage is not possible or is blocked.

Our studies were performed with injectible agents and not inhalation agents. Thus, it is possible that some, or even all of the reduction in anesthetic requirement we observed after hypovolemia was due to a higher concentration of the drug in the blood and brain owing to a reduced volume of distribution. Changes in concentration of the drug at the site of action would depend upon alterations of blood flow to that site relative to differences in blood concentration.[156]

Price[157] predicted that following a single intravenous injection of thiopental, its concentration in the central nervous system would be higher after hemorrhage sufficient to reduce cardiac output by 40%, but insufficient to alter cerebral blood flow, than after a similar injection during normovolemia. This mathematical model assumed that thiopental does not alter tissue blood flow. However, this is not true during hypovolemia. From Price's figure one would estimate that the hypovolemic condition he assumed would reduce the necessary dose of thiopental by approximately one-third. Our finding of a 33 ± 5% reduction in dose of thiopental is in accord with this, although in the other series of hemorrhaged swine in which we did measure cardiac output, it fell by 35%. Bergman[158], in hemorrhaged dogs, found a decreased plasma concentration of thiopental 5-90 minutes after injection over a 2 minute period. Thiopental, however, disappears very rapidly from plasma and richly perfused organs, such as brain. Five minutes after its administration, the concentrations of drug in the central pool and in the rapidly perfused viscera are less than 10% and 50% of their respective peak concentrations;[159] and 60 minutes after injection, concentrations in both compartments are less than 5% of their peak values.[159] Peak brain drug concentration and anesthetic effect occur within the first 2 minutes after injection. Because thiopental rapidly leaves the areas of interest, attempts to extrapolate from small concentrations measured much later, would be subject to error. This would be further compounded as the drug's effect on hemodynamics changed with changing concentrations in various compartments. Bergman did not measure the dogs' blood pressure or cerebral blood flow. It is possible that with the fall in blood pressure that likely occurred after thiopental administration to his hypovolemic animals, cerebral blood flow fell, thus decreasing washout of the drug, resulting in lower plasma concentrations. This is possible because within 15-45 seconds after injection concentration of the drug in richly perfused tissue is higher than in arterial plasma.[159,160] Unfortunately, we did not measure drug concentrations in either plasma or brain, and thus, cannot confirm or refute Price's predictions or our speculations.

5. Determination of minimal alveolar anesthetic concentration (MAC) of halothane and nitrous oxide in swine.

This study was just completed. The minimal anesthetic requirement of swine for halothane and nitrous oxide is greater than that for man and most often laboratory animals[132]. Variability of anesthetic requirement among species has never been adequately explained[151]. Our study did not have the goal of explaining these differences, but rather had the pragmatic aim of establishing the anesthetic requirement of our laboratory animals for these anesthetic agents. The accomplishment of this goal allows us to appropriately conduct other studies.

6. Evaluation of nitrous oxide for induction of anesthesia during hypovolemia.

Although nitrous oxide has been thought to have minimal cardiovascular effects during normovolemia (17-37), we have found that 5 minutes after induction of anesthesia in hypovolemic swine, nitrous oxide caused cardiovascular decompensation for hemorrhage similar to that of halothane. Although nitrous oxide caused a further increase in norepinephrine, the decrease in systemic vascular resistance, cardiac output, mean arterial blood pressure were not different from those animals receiving halothane. Oxygen consumption did not differ between the two groups and both groups demonstrated a similar increase in blood lactate concentration.

Swine anesthetized with nitrous oxide, however, in comparison with those anesthetized with halothane, showed substantially greater recovery of compensation for hemorrhage. This recovery is of interest, and should be the subject of further investigation.

Full discussion awaits return of further biochemical enzymatic assays, and statistical analyses.

7. Importance of the renin-angiotension system during hypovolemia.

This study has just been completed and biochemical and enzymatic analyses are proceeding, as is statistical testing. From the systemic vascular resistance data thus far analyzed, it is clear that despite the published literature (see introduction pp12-13) the renin-angiotensin system does not exhibit an important response 30 minutes after hemorrhage, in awake animals.

E. Conclusions

1. The swine is an excellent laboratory model for the study of hemorrhage. Its cardiovascular system and response to hemorrhage are more similar to those of man than other laboratory animals. When used at a young age, the animal is sufficiently large to instrument fully, yet not so large as to make difficult their handling, housing, or care. Our animals, furthermore, are specific pathogen free; therefore, quarantine upon arrival at the facility is not required thus eliminating unproductive quarantine time and diminishing housing costs. Since our supplier artificially inseminates all sows, breeding is controlled and although strains are not extraordinarily inbred as are experimental mice and rats, the genetic makeup of the animals very closely resemble one to another, thus making results more reproducible than they would be in random source dogs, sheep, goats or other similar animals.

2. Comparison of ketamine, thiopental, enflurane, halothane, and isoflurane for induction of anesthesia during moderate hypovolemia.

a. Ketamine and thiopental.

Both of these injectable anesthetic agents cause similar, important deterioration of cardiovascular compensation for moderate hemorrhage. Reductions in systemic vascular resistance, mean systemic blood pressure, and cardiac output are not different in hypovolemic animals in whom anesthesia is induced with thiopental in comparison with those in whom anesthesia is induced with ketamine. Both agents also further exaggerate the lactic acidosis seen with hemorrhage. A potentially important difference is the continued progressive lactic acidosis one half hour after induction seen in ketamine induced animals but not in thiopental induced animals. We conclude that induction of anesthesia in hypovolemic condition with ketamine does not offer any advantage over induction of anesthesia with thiopental in a similar circumstance. The progressive lactic acidosis seen only in the ketamine group implies that these animals had either less good tissue perfusion, or decreased hepatic perfusion, or both.

b. Enflurane, halothane and isoflurane.

These inhalation agents all cause deterioration of cardiovascular compensation for hemorrhage, similar to the deterioration seen with the injectable agents, ketamine or thiopental. The decrease in systemic vascular resistance, cardiac output, and mean systemic blood pressure among the animals receiving the three inhalation agents are quite similar, as are the metabolic sequelae and increased acidosis.

3. Swine acid-base curve and alignment nomograms differ from those of man and dog, the only two other species for which these nomograms have been constructed. The swine nomograms should be used when evaluating swine acid-base balance.

4. Determination of anesthetic dose of ketamine or thiopental in hypovolemic swine.

Hypovolemia decreases the minimal anesthetic requirement of the two injectable agents studied (ketamine, thiopental). The reduction in minimal amount of anesthetic required was not different for the two drugs.

5. Determination of minimal alveolar anesthetic concentration (MAC) of halothane and nitrous oxide, in swine.

The minimal alveolar concentration for halothane and nitrous oxide in the swine was somewhat higher than most laboratory animals. Therefore, planned studies with swine, and data obtained from anesthetized swine, must be evaluated with this information about their anesthetic requirement in mind.

6. Evaluation of nitrous oxide for induction during hypovolemia.

When used for inducing anesthesia during the condition of moderate hypovolemia, nitrous oxide causes cardiovascular decompensation for hemorrhage, and lactic acidosis similar to that seen with other inhalation anesthetic agents. Cardiovascular recovery during the ensuing thirty minutes appears to be greater with nitrous oxide than with other inhalation anesthetic agents.

7.Test of importance of the renin-angiotension system during hypovolemia.

In awake moderately hypovolemic swine, the renin-angiotensin system does not appear to have an important compensatory role. However, this may not be so during anesthesia.

F. Recommendations:

1. Swine should be considered for increased use for studies involving hemorrhage.
2. The author should (and will) describe the findings thus far in the appropriate medical/scientific literature.
3. USAMRDC should consider providing to the appropriate agencies (? Academy of Health Sciences; ? consultant for anesthesia to the Surgeon General) the conclusions (2a,b;4) regarding use of ketamine, thiopental, enflurane, halothane, and isoflurane during hypovolemic conditions.
4. Studies regarding the cardiovascular and metabolic effects of use of nitrous oxide for induction of anesthesia during hypovolemia should proceed. Results from this study will allow us to provide recommendations regarding the use of nitrous oxide for hypovolemic soldiers, and perhaps afford the opportunity to allow for decreasing the battlefied medical logistical burden (supply of nitrous oxide).
5. Investigations regarding the role(s) of the renin-angiotensin system and vasopressin in compensation for hemorrhage should proceed. The knowledge from these studies is essential for the understanding of normal response to hemorrhage, and how anesthetic agents cause deterioration of that compensatory response.
6. Studies regarding deterioration of compensation for hemorrhage with induction of anesthesia should proceed. These offer the opportunity to improve casualty management of induction of anesthesia during hypovolemia.
7. New anesthetic agents should be evaluated for their efficacy for inducing anesthesia during hemorrhage.

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9. Tables and Figures

Legends for Tables and Figures

1. N=76.

   Values are means ± SE.

   PWP, pulmonary artery wedge pressure; BPa, mean systemic arterial blood pressure; PAP, mean pulmonary artery pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

2. N=7 per group.

   Values are means ± SE.

   RAP, mean right atrial pressure; VO_2 oxygen consumption; triangle BE, change in base excess from previous state; triangle LAC, change in blood lactate concentration from previous state. Other abbreviations same, same as table 1.

   KCT means that K is not statistically different from C, nor is C different from T, but that K is statistically different from T.

3. Groups: C, control, no anesthetic agent; H, halothane; E, enflurane; I, isoflurane.

   Data are means for 7, group C; 7, group H; 8, group E; 8, group I.

   Abbreviations and units as in tables 1 and 2.

4. Data for swine curve nomogram.

5. Mean acid base curve nomogram for swine. See text for derivation of "mean" values for four swine and construction of nomogram.

6. Comparison of our "mean" data for swine (0---0) with Siggaard-Andersen's data for humans (/\---/\) and Scott Emuakpor's data for canines (1---1).

7. Mean acid base alignment nomogram for swine. See text for derivation of "mean" data and construction of nomogram.

8. Data are mean ± SE. N=4 per group. *Statistically different ($p<0.05$) from normovolemic state).

9. Abbreviations and units, same as tables 1 and 2. N=10; values, mean ± SE.

10. N=10; values, mean ± SE. Abbreviations and units same as tables 1 and 2.

11. N=10; values ,mean±SE. Abbreviations and units same as tables 1 and 2.

12. N=5 per group. Values, mean ± SE. Abbreviations and units same as tables 1 and 2.

13. Response, during normovolemia of systemic vascular resistance to angiotensin II and blockade of angiotensin II. Values are mean ± SE. N=5 per group. Abbreviations: A II, angiotensin II; sara, saralasin.

14. Response of systemic vascular resistance to hemorrhage in unanesthetized swine. N=5 per group; values are means ± SE. N, normovolemic; H, hypovolemic.

15. Respones of systemic vascular resistance in awake hypovolemic swine, to angiotensin II and blockade of angiotensin II. N=5 per group. Values are means ± SE. Abbreviations as in figure 13.

Table 1: Awake Swine Response to 30% Hemorrhage

	Normovolemia	Hypovolemia	P
Mean right atrial pressure (torr)	1.3±0.2	-0.2±0.2	<0.001
PWP (torr)	2.6±0.1	0.3±0.2	<0.001
Plasma renin activity ($ng.ml^{-1}.hr^{-1}$)	2.7±0.3	8.7±1.1	<0.001
Plasma epinephrine (pg/ml)	265±23	737±65	<0.001
Plasma norepinephrine (pg/ml)	242±20	452±50	<0.001
Heart rate (beats/min)	113±3	157±6	<0.001
Stroke volume (ml/kg)	1.68±0.04	0.80±0.04	<0.001
Cardiac output ($ml.min^{-1}.kg^{-1}$)	181±3	112±3	<0.001
BPa (torr)	130±2	98±3	<0.001
PAP (torr)	13.5±0.2	9.6±0.3	<0.001
Oxygen consumption ($mlO_2.min^{-1}.kg^{-1}$)	7.53±0.16	8.05±0.19	<0.002
Base-excess (mmol/l)	5.3±0.3	3.1±0.3	<0.001
Blood lactate (mmol/l)	1.1±0.1	1.8±0.1	<0.001
SVR ($torr.l^{-1}.min$)	35.3±0.7	43.8±1.4	<0.001
PVR ($torr.l^{-1}.min$)	2.96±0.08	4.16±0.14	<0.001

n=76. Values are mean ± SE

PWP, pulmonary arterial wedge pressure; BPa, mean systemic arterial blood pressure; PAP, mean pulmonary artery pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

Table 2. Response of Swine to Induction of Anesthesia

	5 min after induction			
	No anesthetic	Ketamine	Thiopental	Statist. interpret.
RAP (mmHg)	-0.3 ± 0.8	-1.2 ± 0.7	0.2 ± 0.2	ns
PWP (mmHg)	0.0 ± 0.4	0.1 ± 0.6	1.9 ± 1.0	ns
Renin activity ($ng \cdot ml^{-1} \cdot h^{-1}$)	6.8 ± 2.8	28.7 ± 5.2	8.9 ± 4.3	K>T,C
Epinephrine (pg/ml)	285 ± 70	2657 ± 987	690 ± 310	K>T,C
Norepinephrine (pg/ml)	209 ± 62	660 ± 220	287 ± 170	K>T,C
Heart rate (beats/min)	162 ± 24	113 ± 11	116 ± 19	ns
Stroke volume (ml/kg)	0.79 ± 0.11	0.76 ± 0.10	0.74 ± 0.14	ns
Cardiac output ($ml \cdot min^{-1} \cdot kg^{-1}$)	117.9 ± 8.9	76.9 ± 5.1	74.0 ± 5.9	C>K,T
BPa (mmHg)	97.2 ± 9.4	41.4 ± 3.5	52.1 ± 7.8	C>T,K
PAP (mmHg)	8.5 ± 0.7	6.7 ± 0.8	8.1 ± 0.6	ns
$\dot{V}_{O_2}$ ($ml\ O_2 \cdot min^{-1} \cdot kg^{-1}$)	7.84 ± 0.55	6.91 ± 0.44	6.80 ± 0.32	ns
Blood lactate (mmol/l)	1.43 ± 0.37	2.78 ± 0.39	2.12 ± 0.37	$\overline{K \backslash T \ C}$
SVR ($mmHg \cdot l^{-1} \cdot min$)	42.3 ± 4.9	29.4 ± 2.9	33.3 ± 3.5	C>T,K
PVR ($mmHg \cdot l^{-1} \cdot min$)	3.67 ± 0.25	4.82 ± 0.38	3.91 ± 0.93	ns
ΔBE (mmol/l)	0.4 ± 0.5	-0.6 ± 0.5	-0.1 ± 0.5	ns
ΔLac (mmol/l)	-0.01 ± 0.06	0.55 ± 0.23	0.65 ± 0.24	C<K,T

e to Induction of Anesthesia during 30% Hypovolemia

duction		30 min after induction			
iopental	Statist. interpret.	No anesthetic	Ketamine	Thiopental	Statist. interpret.
.2 ± 0.2	ns	-0.4 ± 0.7	-1.4 ± 0.5	0.4 ± 0.4	ns
.9 ± 1.0	ns	0.2 ± 0.4	0.4 ± 0.6	0.9 ± 0.4	ns
.9 ± 4.3	K>T,C	8.0 ± 2.6	17.7 ± 4.6	5.3 ± 2.2	$\overline{K}$ C $\overline{T}$
90 ± 310	K>T,C	534 ± 246	2139 ± 1612	453 ± 142	K>C,T
17	K>T,C	459 ± 132	598 ± 367	191 ± 101	$\overline{K}$ C $\overline{T}$
16 ± 19	ns	164 ± 23	121 ± 12	121 ± 18	ns
4 ± 0.14	ns	0.84 ± 0.13	1.01 ± 0.07	0.86 ± 0.09	ns
.3 ± 5.9	C>K,T	123.5 ± 7.6	112.9 ± 9.0	100.8 ± 5.5	ns
.1 ± 7.8	C>T,K	107.5 ± 7.4	79.7 ± 9.1	77.3 ± 10.9	C>T,K
.1 ± 0.6	ns	9.9 ± 1.0	8.3 ± 1.0	9.6 ± 13	ns
1 ± 0.32	ns	7.33 ± 0.33	7.40 ± 0.70	7.18 ± 0.26	ns
.2 ± 0.37	$\overline{K}$ T $\overline{C}$	1.42 ± 0.58	3.31 ± 0.45	2.11 ± 0.36	K>T,C
.3 ± 3.5	C>T,K	45.2 ± 5.0	36.3 ± 4.6	36.6 ± 3.9	C>T,K
1 ± 0.93	ns	4.05 ± 0.55	3.57 ± 0.30	4.26 ± 0.40	ns
.1 ± 0.5	ns	0.2 ± 0.5	-1.5 ± 0.7	0.1 ± 0.6	C,T>K
5 ± 0.24	C<K,T	0.00 ± 0.04	0.53 ± 0.17	-0.01 ± 0.16	T,C<K

Table 2 (continued)--Footnotes:

Values are means ± SE; n = 7 per group.
Group C, no anesthetic; Group K, ketamine; Group T, thiopental.
RAP, mean right atrial pressure; PWP, pulmonary arterial wedge pressure; BPa, mean sy
pulmonary arterial blood pressure; $\dot{V}_{O_2}$, oxygen consumption; SVR, systemic vascular resista
ΔBE, change in base excess from previous state; ΔLac, change in blood lactate concentrati

$\overline{K}$ C $\overline{T}$ means that K is not statistically different from C, nor is C different from T,

pental.

l wedge pressure; BPa, mean systemic arterial blood pressure; PAP, mean

VR, systemic vascular resistance; PVR, pulmonary vascular resistance;

in blood lactate concentration from previous state.

, nor is C different from T, but that K is statistically different from T.

Table 3. Response of swine to induction of anesthesia with enflurane, halothane, or isoflurane during 30% hypovolemia

		Induction of Anesthesia							
	Awake	5 min				30 min			
	Hypovolemic	C	H	E	I	C	H	E	I
BPa	97	97	36	28	29	108	55	45	43
Q	111	118	67	65	61	124	88	86	91
HR	155	162	145	150	121	164	150	152	137
SVR	44	42	26	21	25	45	30	24	26
EPI	746	285	833	426	469	534	712	383	332
NEPI	463	209	249	291	121	459	266	301	124
Renin	9.1	6.8	23	17	26	8.1	30	16	18
Δ Lactate	+0.7	-0.0	+0.6	+1.4	+0.9	0	-0.1	-0.4	0

Table 4. Swine base-excess curve nomogram

Base excess (meq_l^{-1})	Coordinates pH (Units)	Coordinates P_{CO_2} (torr)
-20	7.145	19.7
-19	7.162	20.7
-18	7.178	21.8
-17	7.194	22.9
-16	7.208	24.1
-15	7.223	25.2
-14	7.236	26.3
-13	7.249	27.5
-12	7.262	28.6
-11	7.275	29.8
-10	7.287	30.9
- 9	7.298	32.0
- 8	7.310	33.1
- 7	7.321	34.1
- 6	7.333	35.1
- 5	7.344	36.1
- 4	4.355	37.0
- 3	7.366	37.9
- 2	7.377	38.6
- 1	7.389	39.4
0	7.400	40.0
+1	7.412	40.6
2	7.424	41.0
3	7.436	41.4
4	7.448	41.6
+5	7.461	41.8
6	7.474	41.8
7	7.488	41.8
8	7.502	41.6
9	7.517	41.3
+10	7.532	40.9
11	7.548	40.4
12	7.565	39.8
13	7.582	39.1
14	7.600	38.3
+15	7.618	37.4
16	7.637	36.4
17	7.657	35.3
18	7.678	34.2
19	7.700	33.0
+20	7.722	31.7

FIG 5

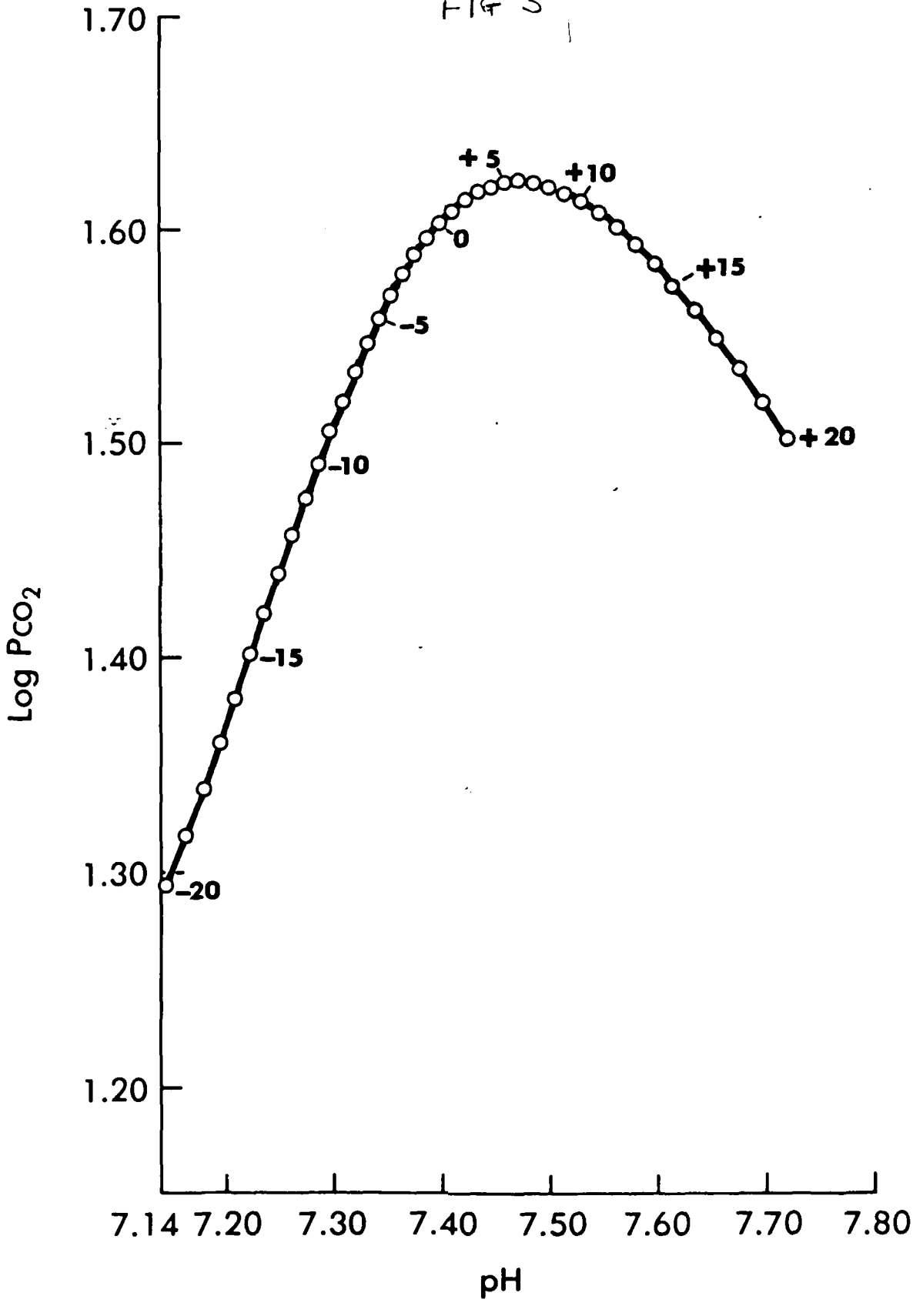

1.70
1.60
1.50
1.40
1.30
1.20
Log P_{CO_2}
+5
+10
0
+15
-5
+20
-10
-15
-20
7.14 7.20 7.30 7.40 7.50 7.60 7.70 7.80
pH

FIG 6

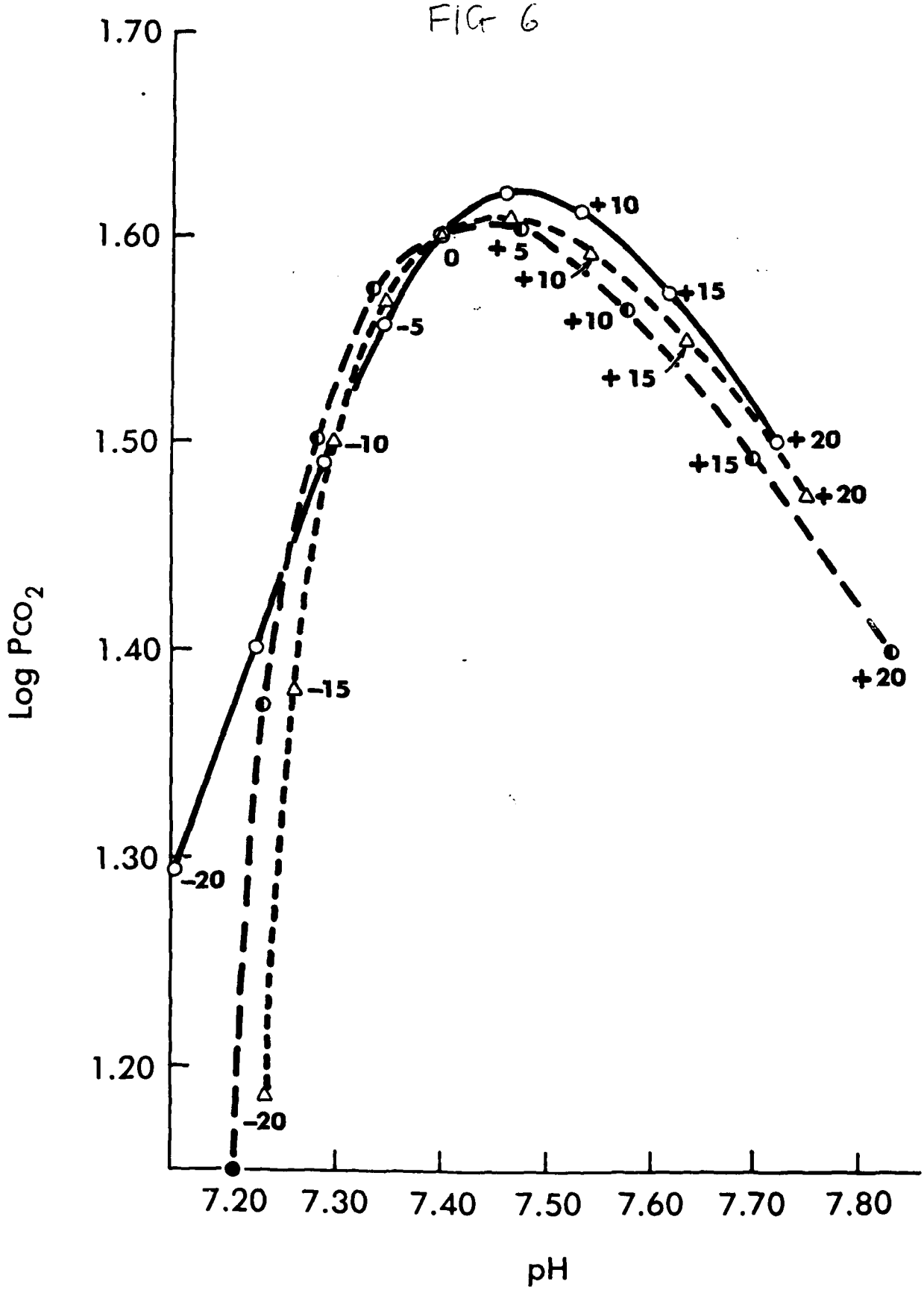

1.70
1.60
1.50
1.40
1.30
1.20
Log P_{CO_2}
7.20
7.30
7.40
7.50
7.60
7.70
7.80
pH
-20
-15
-10
-5
0
+5
+10
+10
+10
+15
+15
+15
+20
+20
+20
-20

FIG 7

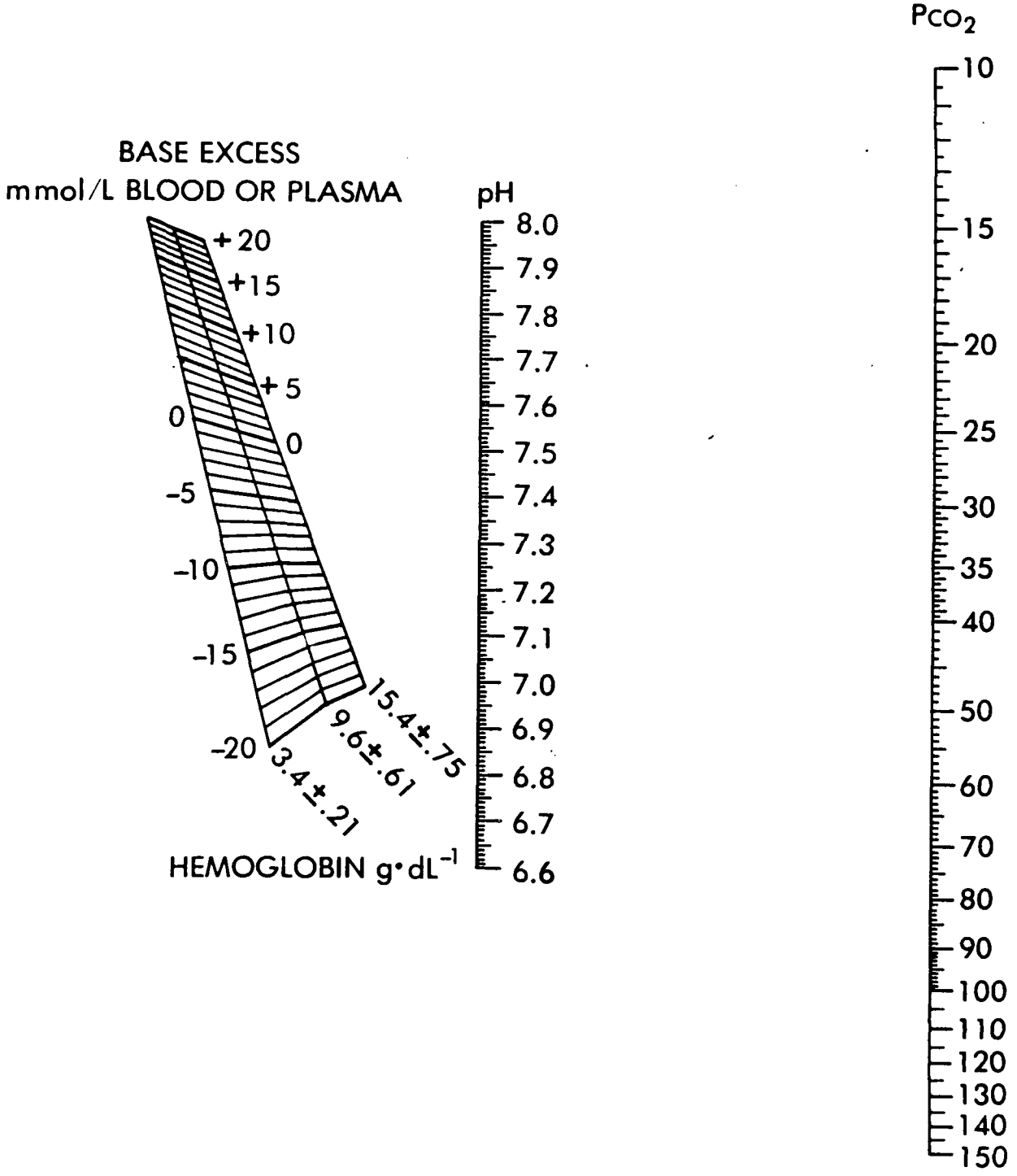

BASE EXCESS
mmol/L BLOOD OR PLASMA
+20
+15
+10
+5
0
-5
-10
-15
-20
15.4±.75
9.6±.61
3.4±.21
HEMOGLOBIN g•dL⁻¹
pH
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
7.0
6.9
6.8
6.7
6.6
PCO2
10
15
20
25
30
35
40
50
60
70
80
90
100
110
120
130
140
150

Table 8. Minimal Anesthetic Dose of Ketamine and Thiopental in Swine during Normovolemia and after Hemorrhage

Drug	Minimum Anesthetic Dose (mg/kg) During Normovolemia	Minimum Anesthetic Dose (mg/kg) During Hypovolemia	Reduction in minimum anesthetic dose during hypovolemia (%)
Ketamine	17.50±0.72	10.31±0.60*	40±5
Thiopental	11.25±1.02	7.50±0.72*	33±5

Data are mean ± SE.

n = 4 per group

*Statistically different ($P < 0.05$) from normovolemic state.

Table 9: Response to 30% hemorrhage in awake swine used for evaluation of use of N_2O for induction of anesthesia during hypovolemia

	Normovolemia	Hypovolemia	P
BPa	133±3	100±5	<0.001
Cardiac output	192±5	121±6	<0.001
HR	128±6	182±9	<0.001
SV	1.55±0.07	0.69±0.05	<0.001
SVR	33.7±1.5	40.3±2.2	<0.005
Blood lactate	1.12±0.14	1.56±0.17	<0.02
$\dot{V}_{O_2}$	7.74±0.27	8.74±0.37	<0.01
Plasma norepinephrine	335±41	731±66	<0.001
Plasma epinephrine	339±40	677±118	<0.02

Abbreviations and units: same at Table 1.

n=10; values, mean ± SE.

Table 10: Cardiovascular and metabolic responses 5 minutes after induction of anesthesia in hypovolemic swine, using 0.25 MAC halothane (Group I) or 0.25 MAC N_2O (Group II).

	Group I	Group II	P
BPa	39±6	61±10	NS
$\dot{Q}_T$	63±6	84±11	NS
HR	157±15	191±18	<0.05
SV	0.42±0.04	0.45±0.05	NS
SVR	28.7±2.9	36.4±4.3	NS
Lactate	2.88±0.46	2.28±0.26	NS
$\dot{V}O_2$	5.85±0.48	7.20±0.71	NS
Epinephrine	2507±527	2290±824	NS
Norepinephrine	423±88	1332±404	<0.05

n=10; values, mean ± SE

Abbreviations and units: same as Table 1

Table 11: Cardiovascular and metabolic responses 30 minutes after induction of anesthesia in hypovolemic swine, using 0.25 MAC halothane (Group I) or 0.25 MAC N_2O (Group II)

	Group I	Group II	P
BPa	56±6	86±7	<0.02
Q	105±10	111±7	NS
HR	154±15	207±14	<0.001
SV	0.71±0.06	0.55±0.03	<0.05
SVR	26.1±2.3	38.3±4.0	<0.02
Lactate	3.52±0.42	2.84±0.49	NS
$\dot{V}_{O_2}$	7.60±0.57	8.86±0.60	<0.05
Epinephrine	1241±313	1592±623	NS
Norepinephrine	404±73	1203±337	<0.02

n=10; values mean ± SE

Abbreviations and units, same as Table 1.

Table 12. Cardiovascular Response of Awake Hypovolemic Swine to Blockade of Angiotensin II (infusion of saralasin)

	Group I (saline)	Group II (saralsin)	P
BPa	111±7	108±7	NS
HR	164±22	169±9	NS
Q	122±11	113±11	NS
SVR	945±69	995±71	NS
Lactate	2.42±0.60	1.97±0.51	NS
Epinephrine	341±149	287±126	NS
Norepinephrine	254±49	303±64	NS
RA	-1.5±0.4	-1.9±0.3	NS

FIG 13.

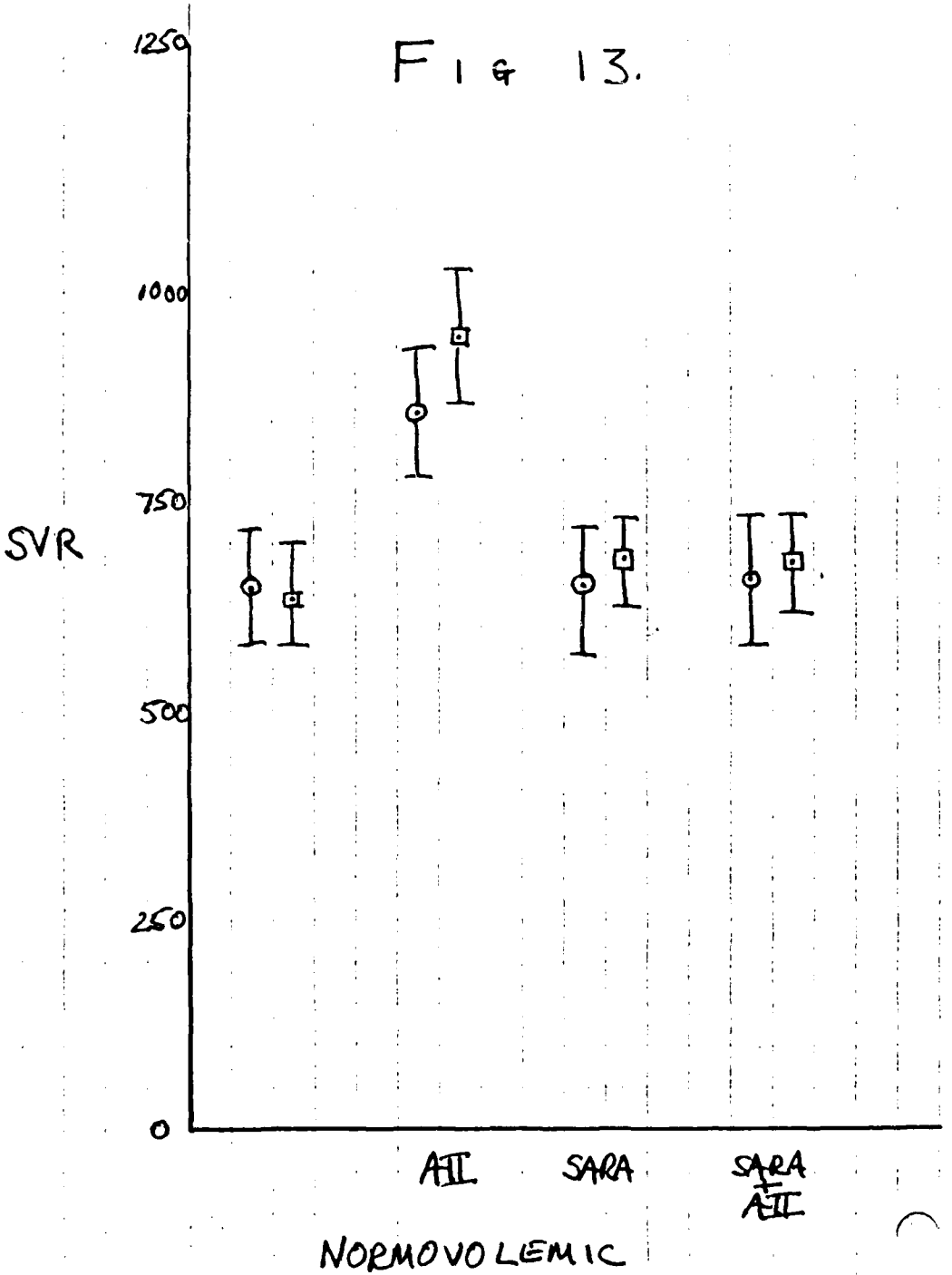

⊙ CONTROL
⊡ EXPERIMENTAL
1250
1000
750
500
250
0
SVR
AII
SARA
SARA + AII
NORMOVOLEMIC

FIG. 14

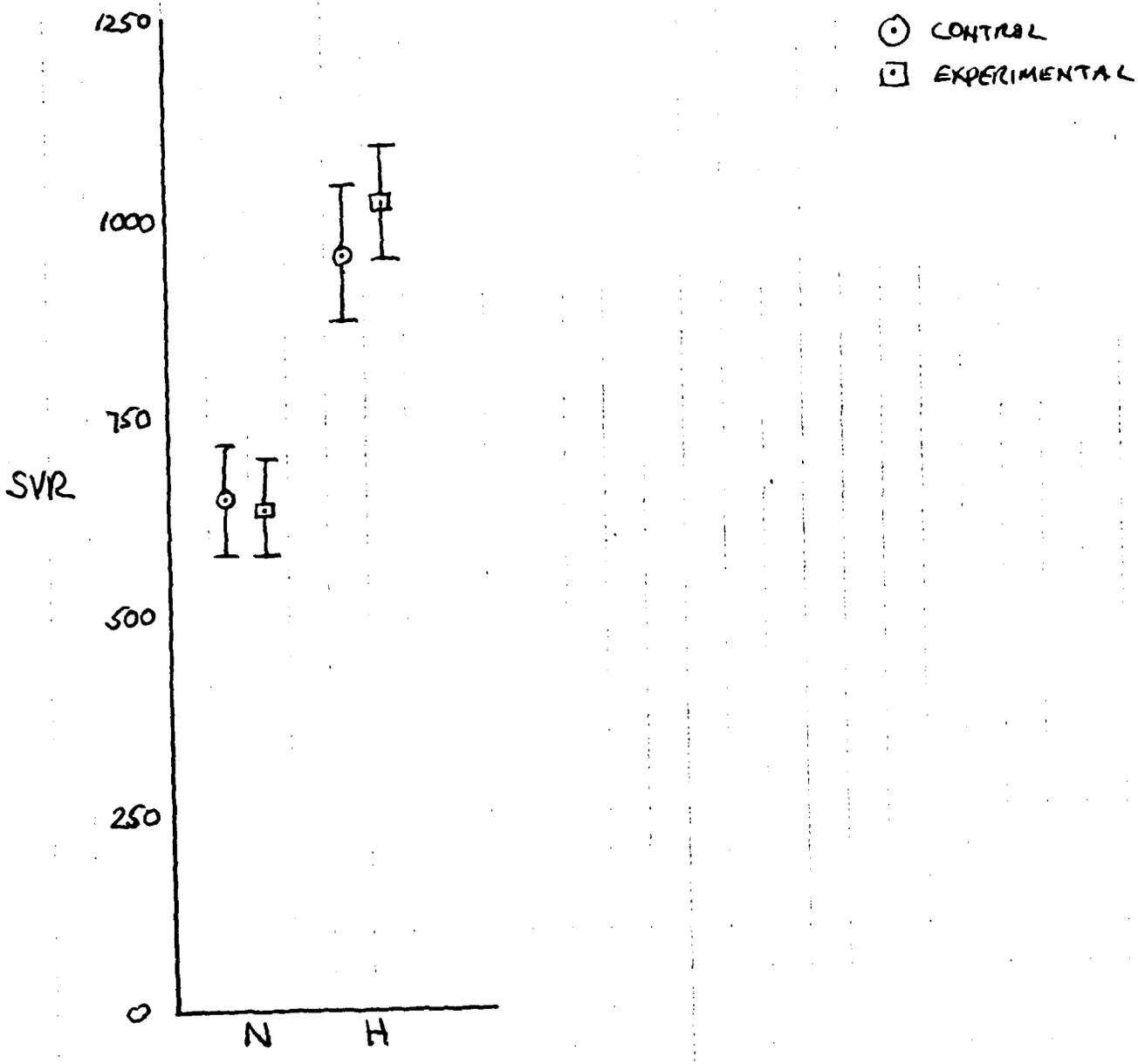
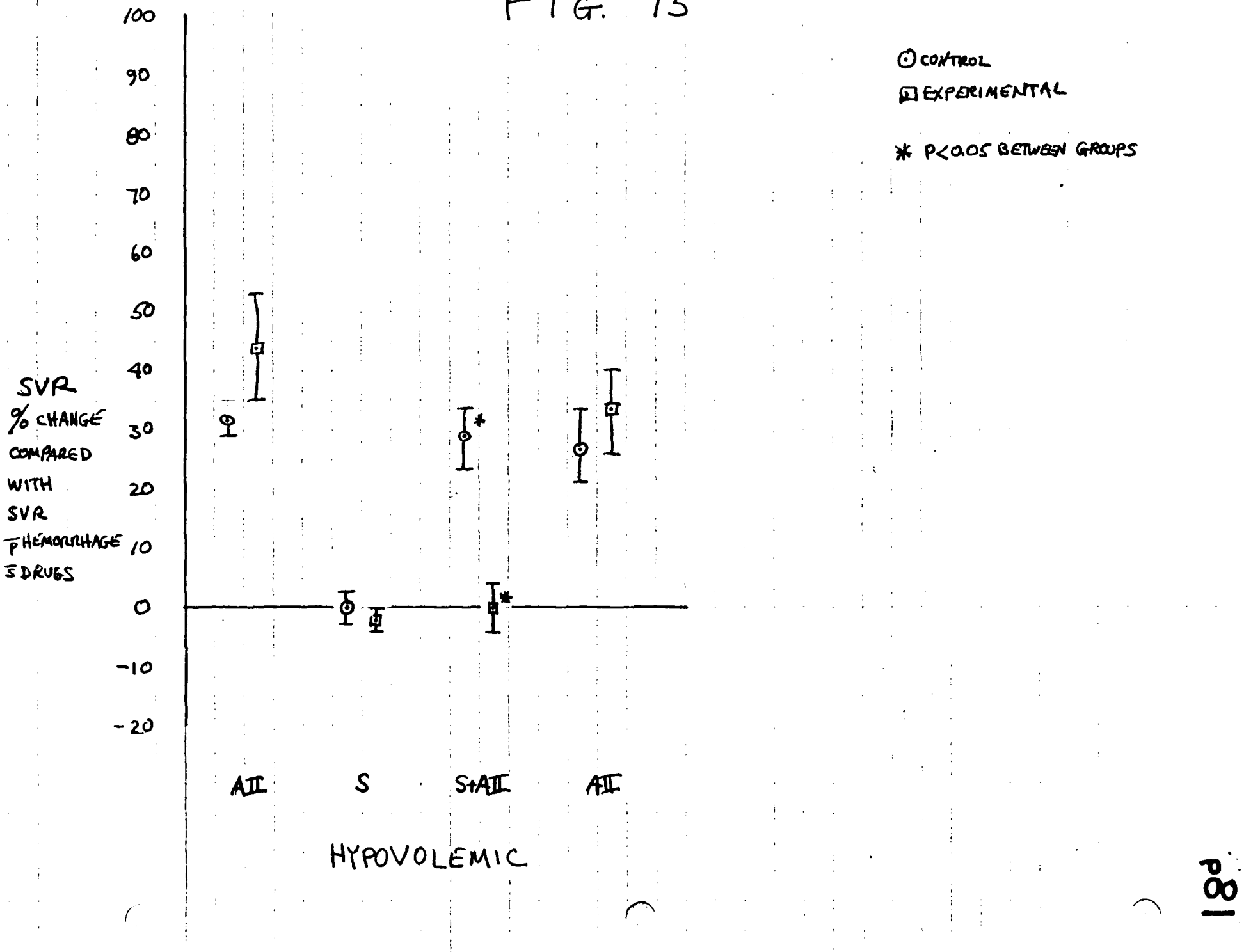


FIG. 15


100
90
80
70
60
50
40
30
20
10
0
-10
-20
SVR
% CHANGE
COMPARED
WITH
SVR
PHEMORRHAGE
DRUGS
AII
S
S+AII
AII
HYPOVOLEMIC
CONTROL
EXPERIMENTAL
* P<0.05 BETWEEN GROUPS

10. Publications Supported by This Contract

1. Weiskopf RB, Townsley MI, Riordan KK, et al: Comparison of cardiopulmonary responses to graded hemorrhage during enflurane, halothane, isoflurane, and ketamine anesthesia. Anesth Analg 60:481-491, 1981

2. Riordan KK, Weiskopf RB, Townsley MI, Chadwick KR: Oxygen-linked hydrogen ion binding of canine hemoglobin. Pflugers Archives 390:99-101, 1981.

3. Weiskopf RB, Fairley HB: Anesthesia for major trauma. Surg Clin North Am. 62:31-45, 1982

4. Weiskopf RB, Townsley MI, Riordan KK, et al: Acid-base alignment and curve nomograms for swine blood. J Appl Physiol 54: 976-983, 1983

5. Bogetz MS, Weiskopf RB, Roizen MF: Ketamine increases catechols, but causes cardiovascular depression and acidosis in hypovolemic swine. Anesthesiology 57:A29, 1982

6. Weiskopf RB, Bogetz MS, Roizen MF, Reid IA: Cardiovascular and metabolic sequelae of inducing anesthesia with ketamine or thiopental in hypovolemic swine. Anesthesiology, in press

ANESTH ANALG
1981;60:481-91

Comparison of Cardiopulmonary Responses to Graded Hemorrhage during Enflurane, Halothane, Isoflurane, and Ketamine Anesthesia

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WEISKOPF, R. B., TOWNSLEY, M. I., RIORDAN, K. K., CHADWICK, K., BAYSINGER, M., AND MAHONEY, E.: Comparison of cardiopulmonary responses to graded hemorrhage during enflurane, halothane, isoflurane, and ketamine anesthesia. Anesth Analg 1981;60:481-91.

To assess the influence of anesthetic agents during mild to moderate hemorrhage, the cardiopulmonary function of five awake, unmedicated dogs was compared with that during anesthesia with enflurane, halothane, isoflurane, and ketamine. Each dog was evaluated during anesthesia with each agent during normovolemia and after blood losses of 10%, 20%, and 30%. Before blood loss, in comparison with the awake state, ketamine increased heart rate (118 ± 11 beats/min, awake, vs 168 ± 17) and cardiac output (5.3 ± 0.4 L/min, awake, vs 6.0 ± 0.2). Halothane and isoflurane did not alter these variables. Enflurane decreased mean arterial blood pressure (110 ± 2 torr, awake, vs 72 ± 3), cardiac output (3.5 ± 0.1 L/min), and stroke volume (46 ± 4 ml, awake, vs 29 ± 2) to a greater extent than did the other anesthetics. Blood loss decreased cardiac output more with ketamine than with the inhalation anesthetics (ketamine, 0.120 L/min/percentage of blood loss; halothane, 0.077; isoflurane, 0.071; enflurane, 0.058; determined by least-squares linear regression, 0–30% blood loss), so that after 30% hemorrhage cardiac output was essentially the same during halothane (2.45 ± 0.19 L/min), isoflurane (2.83 ± 0.19 L/min), and ketamine (2.48 ± 0.15 L/min) anesthesia. Also, during hemorrhage, systemic vascular resistance increased most with ketamine; thus, after 30% blood loss, mean arterial blood pressure was highest with ketamine (ketamine, 94 ± 7 torr; enflurane, 48 ± 5 torr; halothane, 81 ± 4 torr; isoflurane, 58 ± 4 torr). Rate-pressure product and minute work were highest with ketamime throughout hemorrhage, except for minute work after 30% blood loss. These cardiovascular changes were reflected in the measurements of metabolism. Total body oxygen consumption ($\dot{V}_{O_2}$) was highest with ketamine after 0% to 20% blood loss (e.g., after 0% blood loss: ketamine, 8.6 ± 1.2 ml of O_2/min/kg; enflurane, 4.5 ± 0.5; halothane, 4.0 ± 0.3; isoflurane, 4.9 ± 0.6). During blood loss, $\dot{V}_{O_2}$ did not change with any inhalation anesthetic, but decreased with ketamine (6.0 ± 0.5 ml of O_2/min/kg after 30% blood loss); this decrease was associated with an increase in arterial blood lactate concentration and base deficit (ketamine, BE −8.0 ± 0.5 meq/L after 30% blood loss), suggesting that oxygen demand was not met during hypovolemia with ketamine anesthesia. In contrast, lack of change in blood lactate, base deficit, or oxygen consumption during hemorrhage with the inhalation anesthetics suggests that oxygen demand was satisfied when the dogs were bled during enflurane, halothane, or isoflurane anesthesia.

Key Words: ACID-BASE EQUILIBRIUM; ANESTHETICS, Intravenous: ketamine; ANESTHETICS, Volatile: enflurane, halothane, isoflurane; HEMORRHAGE: anesthetics, effects of; METABOLISM: lactate.

HEMORRHAGE stimulates the sympathoadrenal system. Anesthetic agents also may inhibit, stimulate, or have little influence on this system during normovolemia. It is not obvious whether additional stimulation, no effect, or inhibition of the sympathetic system would be most beneficial in anesthetized hypovolemic patients. Hemorrhage has been the subject of many investigations, most using one of the standard "shock" models, in which an experimental

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views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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animal is bled to and maintained at a predetermined arterial blood pressure. Few investigations have used graded, measured hemorrhage as the independent variable.

Although a few limited studies of hemorrhage have used awake human volunteers (1), and some studies have used awake, restrained animals (2), most investigations have used anesthetized animals. These studies usually used injectable anesthetic agents, resulting in varying anesthetic depth during the course of the experiment. When an inhalational anesthetic agent was used, induction of anesthesia was usually accomplished with an injectable anesthetic, or constant end-tidal concentrations were not maintained, resulting in uncertain depth of anesthesia. When the influence of anesthetic agents on hemorrhage has been investigated, failure to remove the spleens of the experimental dogs (3-7) could have allowed uncontrolled and unquantified "autotransfusion" of as much as 35% of the shed blood (8).

Only Theye et al (7) compared in a single study the influence of three anesthetic anesthetics (cyclopropane, halothane, and isoflurane) on cardiovascular function during, and the metabolic consequences of, equivalent graded hemorrhage in dogs. Because they used survival times as their end point, comparing the effects of different anesthetics in the same animal was not possible. They did not remove the spleens, nor did they compare results during hemorrhage with those of awake, unmedicated dogs.

In the present report we have assessed, in hypovolemic dogs in which spleens had been removed, the benefits and disadvantages associated with the administration of anesthetics with differing effects on the sympathetic system. Ketamine, an anesthetic with stimulant-like properties that is frequently recommended for clinical use during hypovolemia, was compared with halothane, which likely inhibits release and activity of catecholamines (9, 10), and with enflurane and isoflurane.

Methods and Materials

We removed the spleens from five healthy mongrel dogs (25 to 32 kg each), previously trained to lie quietly in the laboratory, and provided them with chronic tracheostomies and exteriorized carotid arteries. A minimum of 2 weeks intervened between surgery and the studies. All animals were in good health for each study. All dogs were studied (in random order, separated by a minimum of 2 weeks between successive studies) awake or with 1.15 MAC of the inhalation anesthetics, or with a continuous infusion of ketamine. All animals breathed spontaneously at all times.

For the studies with inhalation anesthetics, the dogs were connected to a circle breathing circuit through a cuffed tracheostomy tube and a non-rebreathing Rudolph valve. Animals received no premedication. Anesthesia for the studies of halothane, enflurane, or isoflurane was induced with the agent to be studied, and was maintained at a constant end-tidal concentration of 1.00% halothane, 2.50% enflurane, or 1.69% isoflurane. The anesthetics were always delivered in a mixture of oxygen and nitrogen that was adjusted to maintain Pa_{O_2} close to 100 torr.

For the studies with ketamine, anesthesia was induced intravenously with 5.0 mg/kg of ketamine, and was maintained by a continuous infusion of ketamine in the smallest amount necessary to prevent gross movement (mean ± SE, 0.25 ± 0.03 mg/kg/min). After the induction of anesthesia, carotid and pulmonary arterial catheters were inserted percutaneously, and the dog was placed in the left lateral decubitus position.

For the awake studies, animals were first anesthetized with thiopental, 7.0 mg/kg; anesthesia was maintained with 70% N_2O in O_2 to allow for placement of carotid and pulmonary arterial catheters. No additional thiopental was administered, and N_2O was discontinued. Animals were studied at least 2 hours after awakening, at which time resting Pa_{CO_2} did not differ from Pa_{CO_2} measured on another occasion before administration of anesthetics or other drugs.

Ventilation was measured by using the rebreathing bag in the circle breathing system as a bag-in-a-box connected to a wedge spirometer (model 570, Med-Science Electronics, Inc). We continuously measured P_{O_2}, P_{CO_2}, and the partial pressure of halothane, enflurane, or isoflurane at the tracheostomy tube orifice by mass spectroscopy (Perkin-Elmer, model MGA 1100A) (11) (Townsley MI, Brinks HA, Weiskopf RB. Measurement of enflurane and isoflurane by mass spectrometry. Abstracts of Scientific Papers, Annual Meeting of the American Society of Anesthesiologists, October 21-25, 1978, Chicago, Illinois, pp 289-90). Carotid and pulmonary arterial pressures were measured by transducers (Statham 23 Db). Mean systemic and pulmonary arterial pressures were derived by a Brush recorder preamplifier. Cardiac output was estimated using a thermodilution technique, a thermistor-tipped pulmonary arterial catheter (Edwards Laboratories), and an analog computer (Gould, model SP1425). Cardiac output measurements were repeated until two successive measurements displaying satis-

factory washout curves differed by no more than 0.2 L/min. This usually occurred within two or three measurements. These physiologic parameters and the partial pressures of the measured gases and vapors were recorded graphically (Gould Brush, model 200, eight-channel polygraph) and magnetically (Hewlett-Packard, model 8868A FM tape recorder). Systemic vascular resistance was calculated as mean systemic blood pressure divided by cardiac output. Pulmonary vascular resistance was calculated as the difference between mean pulmonary artery pressure (PAP) and pulmonary artery wedge pressure divided by cardiac output. Left ventricular stroke work (LVSW) was calculated as the product of mean systolic blood pressure and stroke volume. Left ventricular minute work (LVMW) was calculated as the product of LVSW and heart rate.

Circulatory and ventilatory variables were measured during normovolemia and after 10%, 20%, and 30% reductions in the animal's estimated blood volume (12). Each dog's temperature, measured in the pulmonary arterial blood, was maintained within 1 C of its initial value by the use of circulating water heating pads.

Successive 10% reductions in blood volume were accomplished by drawing blood through the carotid arterial cannula over a period of approximately 10 minutes. The blood was collected into sterile, 600-ml transfer packs containing heparin, so that the final concentration was 3 units of heparin per milliliter of blood. At least 10 minutes of stability was allowed after each reduction in blood volume before beginning measurements at that level of oligemia. Following studies at 30% blood loss, the collected blood was transfused through a microfilter (Pall SQ40SK Ultipor blood transfusion filter); 20 minutes later all measurements were repeated and compared with values obtained before hemorrhage.

During each of the experimental conditions, Pa_{O_2} and Pa_{CO_2} were measured by Radiometer electrodes in steel and glass cuvets; pH was measured by a Severinghaus-UC electrode (13). All electrodes were maintained at 37 C. Calibrating gases and buffers were measured before and after each blood sample reading; the measurement was corrected for electrode drift, liquid-gas factor (14, 15), and the dog's temperature (16). Oxygen concentrations of systemic arterial (Ca_{O_2}) and pulmonary arterial ($C\bar{v}_{O_2}$) blood were measured in duplicate by a galvanic cell instrument (Lex-O_2-Con-TL, Lexington Instruments) (17). Base excess was estimated using a modification of the equations of Severinghaus (18).

During each condition, arterial blood samples were obtained for enzymatic measurement of whole blood lactate concentrations (19).

Results in the normovolemic anesthetized state were compared with results in the awake condition by analysis of variance with repeated measures and by Student's *t*-test for paired data. For each anesthetic, the influence of hemorrhage on the measured and calculated variables was assessed by analysis of variance with repeated measures. Comparison among anesthetic agents at normovolemia and at each level of hemorrhage was accomplished by analysis of variance with repeated measures and by Newman-Keuls method of multiple comparisons. Data obtained in normovolemic, anesthetized state after the return of shed blood were compared with data obtained before hemorrhage using the paired Student's *t*-test (20). In all cases, $p < 0.05$ was considered statistically significant.

As a control, all animals were anesthetized with ketamine for a second time; the same induction and maintenance doses were used. Although no hemorrhage was instituted, all other procedures and measurements were the same as in the first ketamine experiment, including the times at which measurements were performed. Statistical analysis of these data did not indicate significant change in any measured variable with time during ketamine anesthesia.

Results

Awake vs Anesthetized States (during Normovolemia)

Mean (±SE) values for the five normovolemic dogs are presented in Table 1.

All inhalation anesthetics decreased mean arterial blood pressure ($\overline{BP}a$). The increase in $\overline{BP}a$ observed during ketamine anesthesia was not statistically significant. During normovolemia, $\overline{BP}a$ was higher with ketamine than with halothane, which was higher than with isoflurane, which was higher than with enflurane.

Cardiac output ($\dot{Q}$) decreased with enflurane, increased with ketamine, and did not change with halothane or isoflurane. During normovolemia, $\dot{Q}$ was higher with ketamine than with all inhalation anesthetics, and significantly lower with enflurane than with all other agents.

Only ketamine altered (increased) heart rate. Left ventricular stroke volume decreased only with enflurane, and during normovolemia it was higher with

TABLE 1

Comparison of Cardiorespiratory Responses of Five Dogs, Awake and Anesthetized, during Zero Blood Loss*

	Awake	Enflurane	Halothane	Isoflurane	Ketamine
End-tidal concentration (%)	0.0	2.48 ± 0.03	0.99 ± 0.01	1.68 ± 0.01	NA
$\overline{BP}$a (torr)	109.6 ± 2.1	71.8 ± 3.3[d]	99.4 ± 2.3[d]	83.0 ± 7.0[d]	124.0 ± 6.6
HR (beats/min)	118.4 ± 10.8	117.8 ± 2.8	116.0 ± 5.8	125.0 ± 5.5	167.6 ± 17.4[c]
$\dot{Q}$ (L/min)	5.29 ± 0.35	3.45 ± 0.14[c]	4.80 ± 0.18	5.00 ± 0.20	5.97 ± 0.18[c]
SV (ml)	45.6 ± 3.5	29.4 ± 1.6[d]	41.8 ± 2.6	40.1 ± 0.7	37.5 ± 4.8
LVSW (g × m)	5.31 ± 0.47	2.25 ± 0.21[b]	4.41 ± 0.37	3.41 ± 0.31[b]	4.92 ± 0.66
LVMW (g × m/min)	611 ± 37	263 ± 19[d]	506 ± 30	421 ± 27[d]	783 ± 44[c]
$\overline{SVR}$ (torr/L/min)	21.2 ± 1.8	21.0 ± 1.1	20.8 ± 0.5	16.8 ± 1.8	20.8 ± 1.4
$\overline{PAP}$ (torr)	11.2 ± 2.0	14.3 ± 1.4	14.7 ± 1.8	14.5 ± 1.4	14.0 ± 1.6
PVR (torr/L/min)	1.09 ± 0.14	1.62 ± 0.22	1.52 ± 0.18	1.58 ± 0.39	1.85 ± 0.21
$C(a\text{-}\bar{v})_{O_2}$ (ml O_2/dl)	4.2 ± 0.29	3.8 ± 0.35	2.2 ± 0.17[a]	2.8 ± 0.22[b]	4.2 ± 0.53
$\dot{V}_{O_2}$ (ml O_2/min/kg)	7.73 ± 0.48	4.46 ± 0.52[a]	3.95 ± 0.32[a]	4.92 ± 0.55[a]	8.55 ± 1.17
T_{O_2} (ml O_2/min/kg)	32.7 ± 2.4	20.1 ± 1.6[c]	29.7 ± 0.8	29.4 ± 2.0[a]	36.8 ± 1.2
$T_{O_2}/\dot{V}_{O_2}$	4.26 ± 0.28	4.65 ± 0.43	7.76 ± 0.52[b]	6.14 ± 0.49[b]	4.58 ± 0.53
Pa_{O_2} (torr)	97.8 ± 3.8	109.8 ± 3.7[a]	95.9 ± 1.0	107.9 ± 5.2	123.6 ± 8.4
Pa_{CO_2} (torr)	31.3 ± 1.5	49.3 ± 2.8[c]	42.0 ± 2.3[a]	56.2 ± 2.3[b]	32.4 ± 0.9
pHa	7.439 ± 0.011	7.298 ± 0.018[b]	7.336 ± 0.010[b]	7.230 ± 0.022[b]	7.416 ± 0.015
BE (meq/L)	−3.3 ± 0.6	−2.4 ± 0.7	−3.4 ± 1.1	−3.9 ± 0.9	−3.9 ± 0.7
Hct (%)	38.1 ± 0.6	39.3 ± 0.6[a]	38.7 ± 0.5	38.3 ± 1.5	38.8 ± 1.3
Lactate (mM/L)	1.39 ± 0.14	0.33 ± 0.09[b]	1.83 ± 0.28	0.86 ± 0.11[a]	1.75 ± 0.41
PAPw (torr)	5.5 ± 1.7	8.7 ± 1.4	7.1 ± 2.2	7.6 ± 2.5	5.3 ± 1.0
RPP (× 10^3)	16.8 ± 1.1	11.0 ± 0.3[a]	14.5 ± 0.8	13.9 ± 1.2	28.3 ± 2.8[a]
$\dot{V}_E$ (L/min)		3.8 ± 0.5	5.8 ± 0.9	5.7 ± 1.9	14.5 ± 1.1
f, (breaths/min)		9.0 ± 1.8	19.2 ± 4.9	21.9 ± 12.4	39.7 ± 4.4
V_T (L)		0.47 ± 0.04	0.32 ± 0.03	0.37 ± 0.05	0.38 ± 0.06

* Values are means ± SE of five dogs. Abbreviations used are: $\overline{BP}$a, mean arterial blood pressure; HR, heart rate; $\dot{Q}$, cardiac output; SV, stroke volume; LVSW, left ventricular stroke work; LVMW, left ventricular minute work; SVR, systemic vascular resistance; PAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; $C(a\text{-}\bar{v})_{O_2}$, arterial-venous oxygen concentration difference; $\dot{V}_{O_2}$, total body oxygen consumption; T_{O_2}, oxygen transport; Pa_{O_2}, partial pressure of oxygen in arterial blood; Pa_{CO_2}, partial pressure of carbon dioxide in arterial blood; pHa, arterial blood pH; BE, base excess of arterial blood; Hct, hematocrit; PAPw, pulmonary arterial wedge pressure; RPP, rate-pressure product; $\dot{V}_E$, expired minute ventilation; f, respiratory frequency; V_T, tidal volume; NA, not applicable. Comparison of responses produced by each anesthetic separately with awake state: [a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.005$, and [d]$p < 0.001$. For other statistical information, see Tables 5 and 6.

isoflurane and halothane than with ketamine and enflurane.

LVSWork decreased with isoflurane, and to a greater extent with enflurane. Ketamine and halothane did not alter LVSW; consequently, LVSW was lower with enflurane than with the three other anesthetic agents. Similarly, LVMW declined with enflurane and isoflurane, but increased with ketamine as a result of increased heart rate. Consequently, during normovolemia, LVMW was greater with ketamine than with the three other anesthetics, whereas LVMW was lower with enflurane than with the three other anesthetics.

None of the four agents altered peripheral or pulmonary vascular resistances or mean pulmonary arterial or pulmonary wedge pressures.

Total body oxygen consumption ($\dot{V}_{O_2}$) decreased with all three inhalation anesthetics and did not change with ketamime. Consequently, during normovolemia, $\dot{V}_{O_2}$ was higher with ketamine than with all three inhalation anesthetics. The ratio of oxygen transported to oxygen consumed ($T_{O_2}/\dot{V}_{O_2}$) increased with halothane and isoflurane, but did not change with either ketamine or enflurane. During normovolemia, $T_{O_2}/\dot{V}_{O_2}$ was higher with halothane than with all other agents, and was higher with isoflurane than with either enflurane or ketamine.

None of the anesthetics altered base excess. Blood lactate concentrations decreased significantly with enflurane and isoflurane and did not change with halothane and ketamine. There were no differences in blood lactate concentrations between agents during normovolemia.

Physiologic Sequelae of Hemorrhage

Cardiopulmonary responses to hemorrhage with agents during 10% hypovolemia are shown in Tables 2, 3, and 4.

TABLE 2

Cardiorespiratory Responses of Five Anesthetized Dogs during 10% Blood Loss*

	Enflurane	Halothane	Isoflurane	Ketamine
End-tidal concentration (%)	2.49 ± 0.04	1.00 ± 0.01	1.72 ± 0.02	NA
$\overline{BP}$a (torr)	69.6 ± 2.6	91.8 ± 3.3	77.8 ± 4.4	124.0 ± 5.6
HR (beats/min)	117.4 ± 2.9	104.6 ± 5.3	120.2 ± 2.7	177.8 ± 17.6
$\dot{Q}$ (L/min)	2.92 ± 0.10	3.74 ± 0.08	4.15 ± 0.12	5.11 ± 0.39
SV (ml)	23.8 ± 0.4	36.0 ± 1.7	34.6 ± 1.3	29.8 ± 3.1
LVSW (g × m)	1.74 ± 0.07	3.51 ± 0.28	2.86 ± 0.23	3.86 ± 0.35
LVMW (g × m/min)	215 ± 15	362 ± 15	343 ± 26	672 ± 58
$\overline{SVR}$ (torr/L/min)	23.8 ± 0.7	24.6 ± 1.1	18.7 ± 0.9	24.7 ± 2.0
$\overline{PAP}$ (torr)	12.3 ± 1.3	11.7 ± 1.9	11.9 ± 1.0	11.6 ± 1.9
PVR (torr/L/min)	1.94 ± 0.33	1.47 ± 0.28	1.75 ± 0.26	1.82 ± 0.07
$C(a\text{-}\bar{v})_{O_2}$ (ml O_2/dl)	4.4 ± 0.48	3.4 ± 0.14	3.7 ± 0.37	6.0 ± 0.70
$\dot{V}_{O_2}$ (ml O_2/min/kg)	4.39 ± 0.61	4.70 ± 0.12	5.40 ± 0.53	10.53 ± 1.24
T_{O_2} (ml O_2/min/kg)	16.4 ± 1.6	23.1 ± 0.6	23.0 ± 1.1	31.2 ± 1.9
$T_{O_2}/\dot{V}_{O_2}$	3.92 ± 0.43	4.93 ± 0.17	4.42 ± 0.50	3.08 ± 0.28
Pa_{O_2} (torr)	110.9 ± 3.5	96.9 ± 3.4	105.4 ± 2.6	123.1 ± 5.7
Pa_{CO_2} (torr)	45.2 ± 1.8	42.4 ± 2.1	54.5 ± 3.2	30.0 ± 1.4
pHa	7.328 ± 0.010	7.329 ± 0.012	7.230 ± 0.027	7.401 ± 0.020
BE (*meq*/L)	−2.5 ± 0.6	−3.9 ± 1.0	−4.9 ± 0.6	−5.5 ± 1.1
Hct (%)	38.3 ± 0.6	37.1 ± 0.9	36.4 ± 1.0	37.8 ± 1.1
Lactate (mM/L)	0.34 ± 0.10	1.87 ± 0.24	0.88 ± 0.14	2.57 ± 0.43
PAPw (torr)	6.6 ± 1.6	6.3 ± 1.8	5.2 ± 2.1	5.1 ± 1.0
RPP (× 10^3)	10.4 ± 0.3	12.1 ± 0.5	12.4 ± 0.8	30.5 ± 4.1
$\dot{V}_E$ (L/min)	5.1 ± 0.4	5.1 ± 0.6	4.7 ± 0.9	15.0 ± 1.9
f (breaths/min)	12.0 ± 0.9	15.7 ± 3.9	14.5 ± 5.5	48.2 ± 10.2
V_T (L)	0.43 ± 0.03	0.30 ± 0.02	0.39 ± 0.05	0.34 ± 0.04

* Values are means ± SE. Abbreviations are defined in footnote to Table 1. For statistical information, see Tables 5 and 6.

TABLE 3

Cardiorespiratory Responses of Five Anesthetized Dogs during 20% Blood Loss*

	Enflurane	Halothane	Isoflurane	Ketamine
End-tidal concentration (%)	2.52 ± 0.02	1.02 ± 0.01	1.69 ± 0.02	NA
$\overline{BP}$a (torr)	61.8 ± 3.4	88.8 ± 2.8	69.0 ± 3.3	112.4 ± 7.9
HR (beats/min)	119.6 ± 4.2	113.8 ± 8.9	120.8 ± 4.3	190.2 ± 27.0
$\dot{Q}$ (L/min)	2.38 ± 0.14	3.10 ± 0.14	3.52 ± 0.13	3.58 ± 0.27
SV (ml)	19.9 ± 1.1	27.8 ± 1.9	29.2 ± 1.2	20.2 ± 3.0
LVSW (g × m)	1.31 ± 0.14	2.62 ± 0.25	2.13 ± 0.13	2.61 ± 0.51
LVMW (g × m/min)	157 ± 18	290 ± 11	256 ± 12	468 ± 90
$\overline{SVR}$ (torr/L/min)	26.2 ± 1.4	29.0 ± 1.9	19.8 ± 1.4	32.6 ± 2.3
$\overline{PAP}$ (torr)	10.6 ± 1.2	10.0 ± 1.4	9.2 ± 1.5	9.2 ± 2.1
PVR (torr/L/min)	1.87 ± 0.31	2.36 ± 0.22	1.68 ± 0.18	1.99 ± 0.82
$C(a\text{-}\bar{v})_{O_2}$ (ml O_2/dl)	5.9 ± 0.50	4.0 ± 0.34	4.2 ± 0.21	6.4 ± 0.48
$\dot{V}_{O_2}$ (ml O_2/min/kg)	4.74 ± 0.41	4.49 ± 0.22	5.22 ± 0.44	8.05 ± 1.41
T_{O_2} (ml O_2/min/kg)	13.2 ± 1.5	18.4 ± 0.9	19.0 ± 1.0	20.2 ± 2.4
$T_{O_2}/\dot{V}_{O_2}$	2.82 ± 0.31	4.15 ± 0.33	3.70 ± 0.25	2.69 ± 0.24
Pa_{O_2} (torr)	104.2 ± 3.2	99.5 ± 6.3	103.0 ± 2.9	118.8 ± 7.2
Pa_{CO_2} (torr)	43.4 ± 1.5	42.9 ± 2.3	56.7 ± 3.4	32.2 ± 1.3
pHa	7.340 ± 0.011	7.321 ± 0.013	7.221 ± 0.032	7.361 ± 0.011
BE (*meq*/L)	−2.6 ± 0.5	−4.5 ± 0.9	−4.7 ± 0.8	−7.4 ± 0.8
Hct (%)	36.7 ± 1.2	36.4 ± 1.0	36.3 ± 0.9	36.0 ± 1.0
Lactate (mM/L)	0.43 ± 0.13	1.68 ± 0.24	0.96 ± 0.12	2.76 ± 0.66
PAPw (torr)	5.8 ± 1.6	2.9 ± 1.2	3.6 ± 1.8	6.1 ± 2.1
RPP (× 10^3)	9.6 ± 0.6	12.6 ± 0.4	11.4 ± 0.6	29.4 ± 5.7
$\dot{V}_E$ (L/min)	6.1 ± 1.2	6.8 ± 1.2	5.1 ± 1.0	12.1 ± 2.3
f (breaths/min)	16.7 ± 5.1	19.2 ± 5.2	16.9 ± 6.3	36.8 ± 5.9
V_T (L)	0.39 ± 0.04	0.33 ± 0.02	0.37 ± 0.05	0.33 ± 0.19

* Values are means ± SE. Abbreviations are defined in footnote to Table 1. For statistical information, see Tables 5 and 6.

TABLE 4

Cardiorespiratory Responses of Five Anesthetized Dogs during 30% Blood Loss*

	Enflurane	Halothane	Isoflurane	Ketamine
End-tidal concentration (%)	2.52 ± 0.02	0.98 ± 0.01	1.67 ± 0.02	NA
$\overline{BP}a$ (torr)	48.0 ± 4.8	81.0 ± 3.5	58.0 ± 4.0	94.0 ± 7.2
HR (beats/min)	120.0 ± 5.5	121.0 ± 10.7	124.2 ± 4.4	166.0 ± 11.8
$\dot{Q}$ (L/min)	1.69 ± 0.14	2.45 ± 0.19	2.83 ± 0.19	2.48 ± 0.15
SV (ml)	14.0 ± 0.9	20.7 ± 1.9	24.2 ± 1.2	15.4 ± 2.1
LVSW (g × m)	0.72 ± 0.11	1.79 ± 0.21	1.48 ± 0.10	1.74 ± 0.32
LVMW (g × m/min)	87.7 ± 15.5	208 ± 14	185 ± 14	288 ± 50
SVR (torr/L/min)	28.7 ± 2.4	34.0 ± 3.2	21.0 ± 2.4	38.4 ± 3.2
$\overline{PAP}$ (torr)	9.0 ± 0.9	7.6 ± 1.4	6.9 ± 1.8	6.0 ± 1.9
PVR (torr/L/min)	2.89 ± 0.35	2.06 ± 0.26	1.52 ± 0.40	1.98 ± 0.88
$C(a\text{-}\bar{v})_{O_2}$ (ml O_2/dl)	8.1 ± 0.79	5.5 ± 0.53	5.0 ± 0.58	7.5 ± 1.09
$\dot{V}_{O_2}$ (ml O_2/min/kg)	4.48 ± 0.31	4.82 ± 0.23	4.88 ± 0.19	5.99 ± 0.54
T_{O_2} (ml O_2/min/kg)	9.03 ± 1.34	13.5 ± 0.7	14.1 ± 1.1	12.4 ± 1.0
$T_{O_2}/\dot{V}_{O_2}$	2.00 ± 0.25	2.90 ± 0.24	2.92 ± 0.28	2.17 ± 0.40
Pa_{O_2} (torr)	108.4 ± 3.0	100.0 ± 7.1	102.3 ± 5.2	118.0 ± 10.6
Pa_{CO_2} (torr)	41.9 ± 2.6	42.4 ± 2.1	54.3 ± 3.5	33.3 ± 2.8
pHa	7.345 ± 0.024	7.315 ± 0.011	7.224 ± 0.029	7.336 ± 0.018
BE (meq/L)	−3.4 ± 0.5	−4.7 ± 0.8	−5.7 ± 0.6	−8.0 ± 0.5
Hct (%)	36.3 ± 0.9	36.0 ± 1.7	34.5 ± 0.9	33.0 ± 0.5
Lactate (mM/L)	0.45 ± 0.13	1.79 ± 0.35	0.93 ± 0.17	3.13 ± 0.46
PAPw (torr)	4.0 ± 1.2	2.6 ± 1.2	3.1 ± 1.8	3.8 ± 1.5
RPP ($\times 10^3$)	7.7 ± 0.9	11.9 ± 0.6	9.6 ± 0.6	21.2 ± 3.5
$\dot{V}_E$ (L/min)	7.3 ± 2.9	7.2 ± 1.4	6.3 ± 1.6	10.9 ± 0.9
f (breaths/min)	24.9 ± 13.6	19.2 ± 5.4	21.3 ± 8.5	33.4 ± 6.2
V_T (L)	0.37 ± 0.05	0.39 ± 0.10	0.37 ± 0.05	0.35 ± 0.04

* Values are means ± SE. Abbreviations are defined in footnote to Table 1. For statistical information, see Tables 5 and 6.

analyses of the effects of hemorrhage on each variable are given in Table 5.

Progressive hemorrhage decreased left-sided filling pressure (pulmonary arterial wedge pressure) with the inhalation anesthetics but not with ketamine; stroke volume decreased with all agents. Heart rate did not change with hemorrhage with any anesthetic agent; consequently, $\dot{Q}$ decreased progressively with graded hemorrhage with all agents. Systemic vascular resistance (SVR) increased progressively during graded hemorrhage with all agents but insufficiently to prevent a progressive decrease in $\overline{BP}a$, which occurred with all agents. Similarly, pulmonary vascular resistance increased during blood loss with halothane and enflurane, but did not change with ketamine and isoflurane. Mean pulmonary arterial pressure decreased progressively with hemorrhage with each anesthetic agent.

As $\overline{BP}a$ decreased without alteration in heart rate, both stroke work and minute work progressively decreased during graded hemorrhage with all anesthetics. However, rate-pressure product decreased with the inhalation anesthetics with blood loss, but decreased with ketamine only at the 30% level.

As $\dot{Q}$ progressively decreased with graded hemorrhage, tissue oxygen extraction [arterial-mixed venous oxygen concentration difference, $C(a\text{-}\bar{v})O_2$] increased with all agents. This compensation was adequate with the inhalation anesthetics, but not with ketamine; oxygen consumption did not change with blood loss with the inhalation anesthetics, but decreased with ketamine. Oxygen transport decreased with hemorrhage with all agents, as did $T_{O_2}/\dot{V}_{O_2}$.

Base deficit increased with blood loss with all agents except enflurane. Hemorrhage did not change blood lactate concentrations with the inhalation anesthetics; blood lactate concentrations increased with hemorrhage with ketamine.

No ventilatory measurement (expired minute ventilation, ventilatory frequency, or tidal volume) changed with hemorrhage with any anesthetic. Hematocrit did not change during hemorrhage with halothane or ketamine, but decreased slightly with enflurane and isoflurane.

Comparison among Anesthetic Agents of Physiologic Sequelae of Hemorrhage

Statistical analysis of comparison among anesthetic agents at each level of hemorrhage is presented in Table 6.

TABLE 5

Statistical Analysis of Physiologic Sequelae of Hemorrhage in Five Anesthetized Dogs*

	Enflurane	Halothane	Isoflurane	Ketamine
$\overline{BPa}$	0.001	0.001	0.001	0.001
HR	NS	NS	NS	NS
$\dot{Q}$	0.001	0.001	0.001	0.001
SV	NS	0.001	0.001	0.001
LVSW	0.001	0.001	0.001	0.001
LVMW	0.001	0.001	0.001	0.001
SVR	0.01	0.001	0.05	0.001
$\overline{PAP}$	0.001	0.001	0.001	0.001
PVR	0.001	0.05	NS	NS
$C(a-\bar{v})_{O_2}$	0.001	0.001	NS	NS
$\dot{V}_{O_2}$	NS	NS	NS	0.05
T_{O_2}	0.001	0.001	0.001	0.001
$T_{O_2}/\dot{V}_{O_2}$	0.001	0.001	0.001	0.01
Pa_{O_2}	NS	NS	NS	NS
Pa_{CO_2}	NS	NS	NS	NS
pHa	NS	NS	NS	NS
BE	NS	0.05	0.05	0.01
Hct	0.01	NS	0.01	NS
Lactate	NS	NS	NS	0.01
PAPw	0.001	0.05	0.01	NS
RPP	0.001	0.05	0.01	NS
$\dot{V}_E$	NS	NS	NS	NS
f	NS	NS	NS	NS
V_T	NS	NS	NS	NS

* Values indicate whether or not hemorrhage had a statistically significant effect on indicated variable. p is less than the numerical value shown. NS = $p > 0.05$. Abbreviations are defined in footnote to Table 1.

At each level of oligemia, left-sided filling pressure was higher with ketamine than with halothane, which in turn was higher than with isoflurane, which in turn was higher than with enflurane. Stroke volume was always lower with enflurane and ketamine (no significant difference between the two) than with isoflurane and halothane (no significant difference between the two). Heart rate was always higher with ketamine than with all inhalation anesthetics, which did not differ among themselves. Therefore, cardiac output at normovolemia and during 10% blood loss was highest with ketamine and lowest with enflurane; there was no difference between isoflurane and halothane. However, as blood loss increased, $\dot{Q}$ decreased to a greater extent with ketamine (0.120 L/min/percentage of blood loss; linear regression, $r^2 = 0.99$) than with the inhalation anesthetics (halothane 0.077, isoflurane 0.071, enflurane 0.058 L/min/percentage of blood loss; $r^2 = 0.98$ to 1.00), so that there was no difference in $\dot{Q}$ after 20% blood loss among ketamine (3.58 ± 0.27 L/min), isoflurane (3.52 ± 0.13 L/min), and halothane (3.10 ± 0.14 L/min); or after 30% blood loss among ketamine (2.48 ± 0.15 L/min), isoflurane (2.83 ± 0.19 L/min), and halothane (2.45 ± 0.19 L/min). Cardiac output with enflurane was less at all levels of oligemia than with any other agent. Compensation for the decrease in $\dot{Q}$ by an increase in SVR occurred during hemorrhage with all agents, but to varying degrees. Although there were no differences in SVR among agents before hemorrhage, after 30% blood loss SVR was greatest with ketamine; SVR was greater with halothane than with enflurane, which was greater than with isoflurane. With all agents, compensation was incomplete, and consequently $\overline{BPa}$ decreased progressively with graded oligemia. At all levels of blood loss, $\overline{BPa}$ was always greater with ketamine than with halothane, which was greater than with isoflurane, which was greater than with enflurane.

During normovolemia and at all stages of graded blood loss, no differences in mean pulmonary arterial pressure or PVR occurred among the anesthetic agents. At each stage of graded hypovolemia, stroke work and minute work were least with enflurane. Rate-pressure product was greater with ketamine at every level of blood loss than with all inhalation anesthetics.

Tissue oxygen extraction at all levels of hypovolemia was least with halothane but did not differ among the other agents. Total body oxygen consumption at normovolemia and at 10% and 20% blood loss was higher with ketamine than with the inhalation anesthetics; at 30% hemorrhage, $\dot{V}_{O_2}$ decreased significantly with ketamine. There was no difference in $\dot{V}_{O_2}$ among the agents after 30% blood loss.

These differences in $\dot{V}_{O_2}$ were reflected in arterial blood lactate concentrations and calculated base excesses. In response to hemorrhage, arterial blood lactate concentration increased only when animals were anesthetized with ketamine; after 30% hemorrhage, blood lactate concentration was higher during ketamine anesthesia than during anesthesia with all other agents. Similarly, base deficit increased with hemorrhage during ketamine anesthesia to a greater extent than with the inhalation anesthetics, so that after 10% blood loss, base deficit was higher with ketamine than with halothane and enflurane. After 20% and 30% loss, base deficit was greater with ketamine than with any of the inhalation anesthetics.

Because of their incomplete nature, data from two additional animals have been omitted; these animals died as a result of ketamine studies. During a ketamine experiment one animal died from progressive, uncontrollable hyperthermia and cardiovascular collapse. The other dog died 36 hours after failing to

TABLE 6

Statistical Comparison of Ketamine (K), Halothane (H), Isoflurane (I), and Enflurane (E) at Normovolemia and at Each Level of Hemorrhage in Five Dogs*

	Normovolemia	Blood Loss (%)		
		10	20	30
$\overline{BP}a$	K>H>I>E			
HR	K>I=E=H			
$\dot{Q}$	K>I=H>E		K I H>E	I=K=H>E
SV	I=H>K=E			
LVSW	K=H>I>E		H=K=I>E	
LVMW	K>H=I>E			K=H=I>E
SVR	E=K=H=I	K=H=E>I		K>H>E>I
PAP	NS			
PVR	NS			
$C(a-\bar{v})_{O_2}$	E=K=I>H			
$\dot{V}_{O_2}$	K>I=E=H			K=I=H=E
T_{O_2}	K>H=I>E		K=I=H>E	
$T_{O_2}/\dot{V}_{O_2}$	H>I>E=K	H I E K	H I E K	H=I=E=K
Pa_{O_2}	K E=I H			
Pa_{CO_2}	I>E=H>K			
pHa	K>H>E>I	K>H=E>I	K E H>I	E=K=H>I
BE	E=H=K=I	E>H I K	E>H=I>K	
Hct	NS			
Lactate	NS			
PAPw	K=H> >E	K>H>I>E		
RPP	K>H=I=E			
$\dot{V}_E$	K>H=E=I			
f	K>I=H=E			
V_T	NS			

* Abbreviations are defined in footnote to Table 1; NS, no significant difference among agents. Agents listed in descending order of magnitude; > indicates all agents to left of symbol are statistically ($p < 0.05$) greater than all agents to right. $\overline{a\ b\ c} > d$ indicates *a*, *b*, and *c* are all greater than *d*; *a* is greater than *c*, but not greater than *b*; nor is *b* greater than *c*. Similarly, $\overline{a\ b\ c}\ d$ indicates that the only statistically significant difference is that *a* is greater than *c* and *d*. $\overline{a\ b} = \overline{c\ d}$ indicates that *a* is statistically greater than *c* and *d*, and *b* is statistically greater than *d*.

recover from a ketamine experiment in which, after 30% hemorrhage, $\dot{Q}$ and $\overline{BP}a$ were lower and base deficit was higher than during the comparable period of the halothane experiment in the same dog. No deaths or complications occurred during or after experiments with any inhalation anesthetic.

Discussion

In general, the influence of anesthetic agents in our dogs was similar to that observed by others in dogs (10, 21-29) and in man (30-39) (Kopriva CJ. Hemodynamic effects of intravenous ketamine in patients with coronary artery disease. Abstracts of Scientific Papers. Annual Meeting of the American Society of Anesthesiologists, October 1974, pp 233-4). No other study has directly compared these four anesthetic agents in the same animals, although Miller et al (40) recently compared halothane, enflurane, and ketamine in normovolemic rats. Differences between the two studies may be a result of differences in species and/or experimental protocol.

In comparing these four anesthetics during normovolemia, only ketamine produced cardiovascular stimulation. Enflurane in equi-MAC concentration produced greater cardiovascular depression than either isoflurane or halothane. All inhalation anesthetics decreased total body oxygen consumption, but only halothane and isoflurane reduced oxygen demand more than oxygen supply.

Comparison among Anesthetic Agents of Physiologic Sequelae of Hemorrhage

The cardiovascular stimulation seen with ketamine during normovolemia persisted during hemorrhage. At all levels of blood loss, left heart filling pressure, heart rate, and mean arterial blood pressure were

always greatest with ketamine. Similarly, in response to graded blood loss, SVR increased most with ketamine. However, despite the stimulation, cardiac output decreased more with blood loss during ketamine anesthesia than during anesthesia with any of the inhalation anesthetics. After 30% blood loss, no statistical difference in $\dot{Q}$ occurred among ketamine, isoflurane, and halothane. As a result, minute work, rate-pressure product, and oxygen consumption during hemorrhage were always highest with ketamine. After 30% blood loss, $\dot{V}_{O_2}$ decreased with ketamine, but did not change with the inhalation anesthetics, suggesting that oxygen demand was not met at this level of blood loss during ketamine anesthesia. This hypothesis is supported by the more pronounced changes in base excess in response to hemorrhage with ketamine and by the increase in blood lactate concentrations seen only with ketamine during blood loss. It is well documented that hemorrhage increases sympathetic activity (41). Short-term benefits of such stimulation are obvious: increased cardiac output and mean arterial blood pressure. It is far from clear that the cardiovascular gain is worth the metabolic price.

Our results are in some ways analogous to those of Theye et al (7), who compared survival times during removal of 0 to 40 ml/kg of blood from ventilated dogs with intact spleens who were anesthetized with cyclopropane, halothane, or isoflurane. Before blood loss, cyclopropane resulted in higher cardiac output and mean arterial blood pressure than either halothane or isoflurane. The authors (7) attributed their results to higher arterial concentrations of epinephrine during cyclopropane anesthesia. Their observations, in part, also may have been a reflection of the direct vasoconstrictive action of cyclopropane (42) and/or its lesser net myocardial effects (43). With hemorrhage, $\dot{Q}$ and $\overline{BP}a$ decreased more with cyclopropane than with either inhalation anesthetic, and arterial epinephrine increased more with cyclopropane than with either inhalation anesthetic. Total body oxygen consumption decreased the most, and arterial lactate concentration increased the most with cyclopropane. Survival time was shorter with cyclopropane than with either isoflurane or halothane. Our results with ketamine are similar to those obtained with cyclopropane (7). By anesthetizing our dogs with each anesthetic agent and following an identical hemorrhage protocol each time, we found that ketamine, like cyclopropane, does not appear to be as useful for maintenance of anesthesia during hemorrhage as agents that are not sympathetic stimulants.

Longnecker and Sturgill (44), using rats that were bled to $\overline{BP}a$ of 40 torr for 1 hour, found a higher survival rate in rats anesthetized with ketamine than in those anesthetized with pentobarbital or halothane. Longnecker and Sturgill speculated that ketamine may have increased survival rate in these animals because a balance between oxygen demand and delivery was maintained. However, they did not measure blood gas tensions, cardiac output, regional blood flow, oxygen consumption, or blood lactate concentration. Our dogs required a higher F_{IO_2} to maintain Pa_{O_2} at 100 torr when anesthetized with the inhalation anesthetics than when anesthetized with ketamine. Because Longnecker and Sturgill's rats breathed room air, it is possible that their animals which were anesthetized with halothane were hypoxic. Although we did not measure regional blood flow or metabolism, our total body data do not support the concept that ketamine maintains a balance between oxygen demand and delivery.

The lack of change in heart rate with hemorrhage that we noted has also been observed previously by others (3–5). Reviewing several hundred of his experiments on dogs, Wiggers (45) noted that heart rate response to hemorrhage was somewhat variable. He found that, in general, when heart rate was initially below 100 beats per minute, it increased in response to hemorrhage; that when it was initially 150 beats per minute or greater, it tended to decrease in response to hemorrhage. Inasmuch as the initial heart rates of our dogs were approximately 120 beats per minute, it is not surprising that heart rate did not change with hemorrhage.

In man, duration of anesthesia alters the cardiovascular actions of halothane (33) and enflurane (30, 31) but not of isoflurane (37, 38). There is no evidence that such recovery occurs in dogs. Each of our studies took several hours, the mean time between induction of anesthesia and measurements made after 30% blood loss being 282 minutes. The measurements taken in normovolemic animals during the early part of the anesthetic procedure and those taken late in the anesthetic procedure after return of the shed blood did not differ significantly. Also, during several hours of ketamine anesthesia without hemorrhage, measured and calculated variables did not change. These two facts indicate that no functional mechanism altered cardiovascular function with time during anesthesia.

As our animals breathed spontaneously, Pa_{CO_2} varied among anesthetic agents (Tables 5 and 6). The dogs were mildly hypocarbic with ketamine, hypercarbic with isoflurane, and nearly normocarbic with

halothane and enflurane. Cardiovascular stimulation caused by carbon dioxide is blunted by halothane (35, 36), isoflurane (37), cyclopropane (46), and fluroxene (47). Cardiovascular depression seen with enflurane during controlled ventilation (31) is eliminated when Pa_{CO_2} is allowed to increase with spontaneous ventilation (30). However, after several hours of enflurane anesthesia with spontaneous ventilation in volunteers, Pa_{CO_2} returned to near normal values, but cardiovascular depression did not become evident. Thus, at the time we performed our measurements, it appears that the relationship of cardiovascular stimulation by CO_2 during enflurane anesthesia is altered. It is possible that differences in P_{CO_2} influenced our results. There are no data regarding the interaction of hemorrhage, anesthetic anesthetics, and carbon dioxide; however, the relatively mild hypocapnia seen with ketamine (e.g., P_{CO_2} 33 torr at 30% blood loss) is not likely to have resulted in major hemodynamic changes.

Clinical Implications

Our data suggest that ketamine may be less desirable than halothane or isoflurane for maintenance of anesthesia during moderate hypovolemia. However, it may be inappropriate to translate these studies in animals directly to man. Differences and similarities in the cardiovascular effects of anesthetic agents between man and dog during normovolemia may not be the same during hypovolemia. Finally, our experiments did not study the effects of anesthetics used for induction of anesthesia in the presence of preexisting hypovolemia, and consequently we can make no comment in this regard. The considerations and consequences of producing acute sympathetic stimulation, as during induction of anesthesia, may not be similar to those during the more prolonged maintenance of anesthesia.

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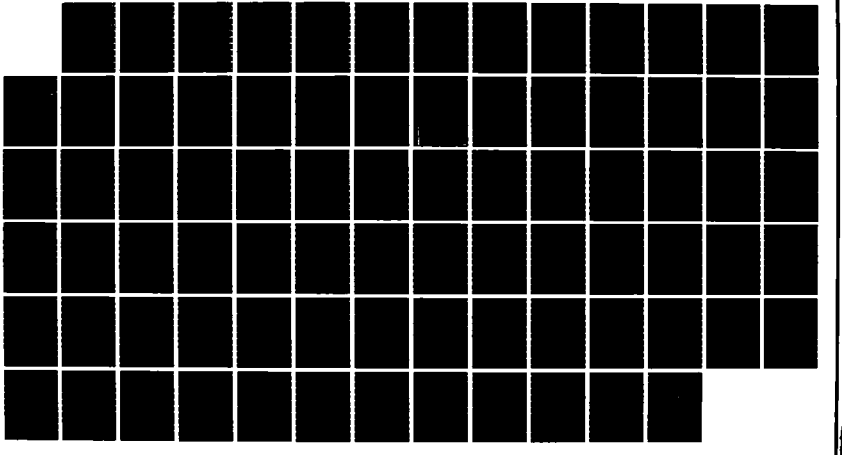

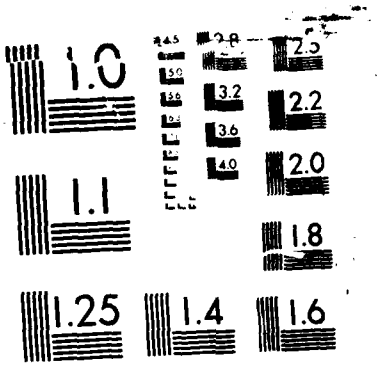

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Oxygen-Linked Hydrogen Ion Binding of Canine Blood

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ABSTRACT: Decrease in hemoglobin oxygen saturation without change of true blood base-excess results in an increase in calculated base-excess because of differences in acidity between oxy- and deoxyhemoglobin. We have determined the mean ± SE canine base-excess correction coefficient to be 0.43 ± 0.01 mmol base per mmol heme, a value approximately 34% higher than the corresponding value for human hemoglobin.

KEY WORDS: acid-base equilibrium; canine blood; carbamino-CO_2; carbon dioxide; canine hemoglobin; hydrogen ion concentration; oxygen

NEW ABBREVIATIONS: base-excess correction coefficient: ·

The preferential binding of CO_2 by deoxygenated blood was first described by Christiansen, Douglas and Haldane.[5] Dill, Edwards, and Consolazio[6] quantified the physiological significance of the Haldane effect and determined that desaturation of hemoglobin changes the base-binding capacity of human blood. When Bauer[2,3] described interaction between 2,3-diphosphoglycerate (2,3-DPG) and the Haldane effect, the base-excess correction factor for hemoglobin desaturation was reexamined by Siggaard-Andersen and Salling.[20]

The alteration of base-excess by oxygen-linked hydrogen ion binding may be expressed as: $\Delta BE = \cdot [Hb] [1 - SO_2]$; where ΔBE is the change in base-excess as a result of hemoglobin desaturation, · is the base-excess correction coefficient, and SO_2 is the fractional saturation of hemoglobin. Siggaard-Andersen and Salling found, in a single subject with normal base-excess and 2,3-DPG concentration, the value for the base-excess correction coefficient to be 0.20 mEq/g when the Hb concentration is expressed in g/dl, or 0.32 mEq/mmol when the Hb concentration is expressed in mmol heme per liter.[20]

Rodkey et al.[13] estimated $\Delta[HCO_3^-]/\Delta[HbO_2]$ for canine blood, but because of the variability in their data and the absence of measurement of 2,3-DPG concentrations, we have estimated, for canine blood, the base-excess hemoglobin desaturation correction factor, · .

METHODS: Fifty milliliters of arterial blood were drawn from each of four healthy dogs into glass syringes containing 1500 IU heparin. One milliliter of each dog's blood was set aside for subsequent determination of 2,3-DPG,[11] hemoglobin,[4] and methemoglobin[7] concentrations. The remaining 49 ml of each sample were divided into 6 ground-glass syringes and placed in ice for later preparation and analysis. The resultant 6 blood samples from each dog were tonometered at 38°C with gases of PO_2 0 or 600 torr and PCO_2 25, 40, or 65 torr. Gases for tonometry were prepared on-line with CO_2, O_2, and N_2 using a gas-mixing flowmeter. PO_2 and PCO_2 of the mixed gas were monitored continuously by mass spectroscopy (Perkin-Elmer MGA 1100A) and adjusted to the desired partial pressures.

Hemoglobin, 2,3-DPG, and oxygen concentrations and PO_2, PCO_2, and pH were measured for each syringe blood sample. All blood tensions were measured at 38°C, in duplicate, with Radiometer electrodes (E5046 and E5036) in Radiometer steel-and-glass cuvettes (D616). Electrodes were calibrated using gas mixtures previously analyzed in triplicate by the method of Scholander.[16] Calibration gases of 0.00% or 90.80% O_2 and 3.33%, 5.20% or 9.57% CO_2 were selected so that calibration was performed with the standard PO_2 or PCO_2 closest to the expected blood gas value. The appropriate calibration gas was measured before and after each blood measurement. The pH of each blood sample was measured at 38°C in duplicate using a Severinghaus-UC pH electrode[18] calibrated with Radiometer precision buffers (pH 7.381 and 6.838) in 3 ml glass ampules. The 7.381 buffer was measured before and after each blood pH measurement. Blood gases and pH were corrected for electrode drift as necessary and PO_2 was also corrected for the blood-gas factor.[9] PO_2 values of fully oxygenated samples were read every 15 s for 5 min after placement of blood into the cuvette. True PO_2 was estimated by plotting PO_2 against time and extrapolating the linear fall of PO_2 to the time of insertion of the blood into the cuvette. The O_2 concentration of each blood sample was measured in duplicate using an electrolytic cell (Lex-O_2-Con-TL, Lexington Instruments).[12]

Log PCO_2 was plotted against pH, and least-squares linear regression lines were drawn through each set of 3 points of equivalent hemoglobin saturations. The base-excess was estimated at the intersection of the computed line and the base-excess curve for dogs as determined by Scott Emuakpor et al.[17] The difference between the estimated base-excess (in mmol/l) of oxygenated blood was used to calculate · (a correction factor without units): · = $\Delta BE/[Hb][1-SO_2]$; where, in keeping with the terminology

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and abbreviations of Siggaard-Andersen and Salling,[20] Hb is the heme concentration in mmol/l after correcting for the presence of methemoglobin.

RESULTS: We determined the mean (± SE) canine base-excess correction factor, , to be 0.43 ± 0.01 mmol base/mmol heme (or 0.27 ± 0.007 mmol base/g Hb). The range of in the four dogs was 0.40 to 0.46. Mean differences (± SD, calculated without regard to sign) between duplicate analyses of all samples was 0.4 (± 0.14) torr at PCO_2 = 25, 0.5 (± 0.27) torr at PCO_2 = 40 torr, and 0.6 (± 0.36) torr at PCO_2 = 65 torr. The mean difference between duplicate pH analyses was 0.0015 (± 0.0013) pH units.

The mean (± SE) slope of the computed linear regression of log PCO_2 vs pH was -1.61 (± 0.04) (range of r^2 = 0.998 - 1.000), which agrees closely with the value of -1.56 (± 0.06) found by Rossi-Bernardi and Roughton.[14]

DISCUSSION:

Effect of Technical Precision on Results: The accuracy of the determination of relies heavily on the technical precision of pH and PCO_2 measurements. The effect of possible errors in the measurement of blood gases on the estimated value of was examined by altering all blood results by one-half the mean differences between duplicate analyses of samples, so as to create a maximum possible change in . New 's were calculated using the methods described above. These calculations resulted in a mean maximal decrease in of 0.026 (± 0.003) or a mean maximal increase in of 0.022 (± 0.005). However, the agreement of our slopes of log PCO_2 vs pH with those published by Rossi-Bernardi and Roughton,[14] the fit of our points by linear regression (range of r^2: 0.998-1.000), and the small variation in the estimated among the four dogs suggest that our error in measuring PCO_2 and pH was considerably less. In our laboratory, using the same procedure and the base-excess curve of Siggaard-Andersen,[19] mean (± SE) of normal human blood is 0.33 (± 0.01), which corresponds closely with the value of 0.32 published by Siggaard-Andersen and Salling.[20]

Each dog's hemoglobin and 2,3-DPG concentrations were measured seven times. The SE for the hemoglobin determinations did not exceed 0.1 mmol/l for any dog. Error in the measurement of hemoglobin concentration should not have created an error greater than 1% in the estimation of . 2,3-DPG concentrations of 3 dogs were found to be within the normal range of 15.4 (± 1.4) µmol per g Hb for dogs.[1] The slightly higher for one dog may have been caused by its somewhat elevated 2,3-DPG. We did not investigate the effect of 2,3-DPG on canine , nor are we aware of such an investigation having been performed by others.

Effect of Changes on PCO_2 and pH on : Although changes in PCO_2 and pH are known to alter , the effect is very small if no acid or base is added and blood base-excess remains constant and near 0. Within the range of our measurements (pH 7.2, PCO_2 65 torr to pH 7.6, PCO_2 25 torr), changes produced in pH and PCO_2 to estimate should have changed by less than 0.003.[20]

Our estimated value of 0.43 for canine blood falls within the range of 0.39 to 0.80 for the $\Delta[HCO_3^-]/\Delta[HbO_2]$ found by Rodkey et al.[13] Dill, Edwards, and Consolazio,[6] although unable to directly measure blood pH, found the correction factor for human blood to be approximately 0.44 mEq/mmol or 0.27 mEq/g at pH 7.3-7.5. However, more recently Siggaard-Andersen and Salling[20] have determined a value for of 0.32 mEq/mmol (or 0.20 mEq/g) for human blood, and we have confirmed that value in our laboratory (unpublished data). Our estimated value of for canine blood is approximately 34% larger than that for human blood.

Use of the human blood value of to correct canine blood base-excess results in a relatively small error in the corrected base-excess value. At 50% desaturation, with a normal canine Hb of 10 mmol/l, use of the human value for instead of the canine value overestimates the true base-excess by approximately 0.6 mmol/l. We do not have a clear explanation for the difference between our canine value and Siggaard-Andersen and Salling's and our own human values. Both human and dog hemoglobins have identical amino acid compositions at the sites that are known to bind CO_2.[8] It is possible that amino acid differences at other locations result in alterations of secondary or tertiary structure of canine hemoglobin, thereby changing its oxygen-linked hydrogen ion binding; however, there is no direct evidence to support this concept. Alternatively, the higher value for in dogs could be a result of greater 2,3-DPG concentration.[1] Normal canine blood 2,3-DPG concentration (15.4 ± 1.4 µmol per g Hb) is greater than that of human blood (11.8 ± 1.4 µmol per g Hb).[1] 2,3-DPG interferes with carbamate formation by terminal NH_2 groups of the beta chains of the Hb molecule, thereby reducing the CO_2 binding capacity of hemoglobin.[3,10,15] Siggaard-Andersen and Salling[20] found that if human blood was depleted totally of 2,3-DPG, the base-excess correction coefficient decreased. Their data only included these two points (normal and 0 DPG) and thus do not allow for detailed assessment of the effect of variation in 2,3-DPG concentration on the value of . Although we did not systematically alter 2,3-DPG concentration, our data appear to support the limited observation of Siggaard-Andersen and Salling[20] that varies directly with 2,3-DPG concentration; this relationship may account, in part, for the higher in dogs in comparison with man.

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Anesthesia for Major Trauma

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This article will emphasize the anesthesiologist's role in the management of patients with major trauma, particularly those features that relate to airway management and fluid resuscitation. Problems peculiar to some of the more common major injuries will also be outlined.

INITIAL EVALUATION AND MANAGEMENT

Airway and Gas Exchange

On arrival in the emergency room, all seriously traumatized patients should receive oxygen, since many physiologic sequelae of trauma result in arterial hypoxemia while the patient is breathing air. The chest should be auscultated bilaterally, and if there is any question of a possible chest injury, radiographs should be obtained immediately. Hemothoraces or pneumothoraces should be relieved by placement of large bore chest tubes. Patients in whom systemic blood pressure is unobtainable require immediate intubation of the trachea and ventilation with 100 per cent oxygen as part of the initial emergency room resuscitation sequence (rapid intravenous fluid administration and, if necessary, thoracotomy and aortic cross-clamping). Fixed, dilated pupils, in and of themselves, are not an accurate indication of irreversible central nervous system damage and do not contraindicate aggressive management at this time.[1, 2] If an esophageal obturator has been previously inserted, it should not be removed until the airway is protected with an endotracheal tube, because of the likelihood of regurgitation of gastric contents and the possibility of subsequent aspiration. Patients who are markedly hypotensive despite rapid intravenous infusion also require early intubation to support gas exchange and protect the airway, since cerebral ischemia commonly causes muscular flaccidity and regurgitation of gastric contents. The decision as to when to intubate a hypotensive awake patient in the emergency room is difficult to make; these patients are usually candidates for immediate surgery because of continuing gross hemorrhage. If anesthesia is necessary for intubation of the trachea, we use a ketamine-succinylcholine sequence described later in this article.

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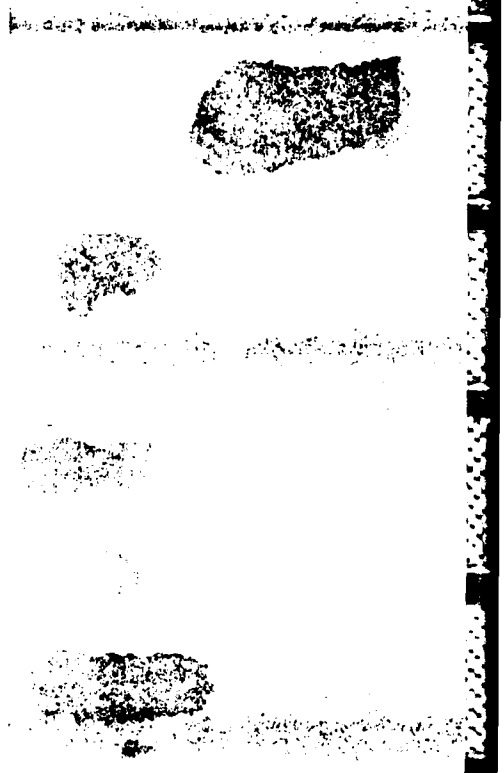
Facial Fractures and Upper Airway Injuries. Airway assessment is the main early requirement in this group of patients. Massive facial injuries may result in nasal obstruction, oropharyngeal edema, and hematomata of such magnitude that immediate tracheotomy or cricothyroidotomy is necessary in the emergency room. In all other cases, the rate of progress of any swelling in the upper airway must be evaluated. The principle is to ensure the maintenance of a patent airway and to avoid frustration of available techniques by "sudden" airway obstruction. In patients with multiple fractures of the mandible and maxilla (LeFort III) in whom massive edema has yet to occur, oral intubation is preferred and is usually easily accomplished, should it be required. In the most obtunded, the trachea may be intubated without anesthesia. If this situation is misjudged, vomiting may occur and strong suction must be *immediately* available. Blind nasal intubation may be hazardous because of potential false passages into nasal sinuses and the cranial vault and the possibility of dislodging loose bone and tissue. It is unusual for an alert, cooperative patient with facial injuries to require intubation in the emergency department. However, if this is necessary, the alternatives for direct laryngoscopy and intubation are (1) topical anesthesia, spraying of an anesthetic, and advancing the laryngoscope in a series of stages or (2) general anesthesia with preoxygenation, cricoid pressure, thiopental or ketamine, and succinylcholine. Fractures of the mandible alone usually do not cause airway difficulties when the larynx is normal.

Injuries of the larynx may cause rapid respiratory obstruction and require immediate tracheotomy. In less urgent situations, and when assessing the possibility of such an injury, a history of trauma to the head and neck, stridor, hoarseness, and crepitus in the neck are all suggestive. The most frequent cause of a fractured larynx is direct force from a deceleration injury. A fracture in the region of C6 or C7 is a common association. Three useful evaluative tests for laryngeal fracture are (1) asking the patient to make a high-pitched "e" sound, which requires mobile cricoarytenoid joints, normal tense cords, and functioning intrinsic laryngeal neuromuscular mechanisms; (2) indirect laryngoscopy; and (3) radiography of the larynx, especially, a computerized axial tomographic (CAT) scan. If uncertainty exists, fiberoptic laryngoscopy may be performed under topical anesthesia. *If this type of injury is suspected,* all possible information should be accumulated prior to induction of general anesthesia, since laryngeal obstruction may occur during attempted tracheal intubation. The latter may cause mucosal stripping, bleeding, or displacement of fractured cartilage into the airway lumen.



When a fractured larynx is present, laryngofissure and repair of mucosal lacerations and cartilage fractures are frequently carried out. Classically, a tracheotomy under local anesthesia is performed first. Alternatively, there are recent reports of successful tracheal intubation through the glottis.[7] This should be attempted only in the presence of the most benign preoperative findings and when laryngeal visualization is excellent. If a tracheotomy is necessary in an uncooperative child, it may be accomplished following a small dose of ketamine as a supplement to local anesthesia.

In all cases of possible airway compromise, when it is uncertain whether the proposed anesthetic maneuvers will be successful, that is, if airway obstruction could occur, the procedures should be carried out in an operating room with equipment and personnel ready for immediate tracheotomy.

Head Injuries. A high percentage of unconscious patients with recent head injuries require intubation for one or more of the following three indications: (1) to overcome airway obstruction, (2) to prevent aspiration of secretions, and (3) to insure

hyperventilation in order to minimize intracranial pressure. If it is decided not to intubate a patient who has a fresh head injury, this individual must be observed closely; personnel able to intubate him or her must be readily available. Sudden rapid deterioration occurs quite commonly within the first few hours and therefore a single evaluation is not sufficient. When possible, cervical films are obtained prior to intubation, although, in our experience, neck fractures are quite rare in patients who require intubation for a head injury. If it is suspected that the neck is unstable a cervical collar is placed, and oral intubation may be attempted using a "hockey-stick" bend at the tip of the endotracheal tube created by means of a stylet. If oral intubation appears technically straightforward, we do not hesitate to use muscle relaxants with application of cricoid pressure, following a period of preoxygenation. The surgeon should hold the head during this intubation and warn of any impending excessive extension. The alternatives are blind nasal intubation, which may be easy in the hyperventilating patient, or, if time permits, intubation over a fiberoptic bronchoscope. If all else fails, tracheotomy may be necessary.

Barbiturates, other hypnotics, or muscle relaxants may be required to control restlessness, either to permit CAT scanning or angiography or to prevent an increase in intracranial pressure owing to straining caused by the irritation of an endotracheal tube. The ability to conduct a neurologic assessment is thereby lessened, but this should not be of concern. Either a surgical decompression is indicated by the radiologic findings, or if not, an intracranial pressure line may be inserted to permit accurate ongoing evaluation.

Fluid Resuscitation

In any patient in whom a major injury is suspected, at least two large bore intravenous cannulae should be inserted, one of which should be located centrally (superior vena cava or right atrium). One should not depend upon lower extremity lines for infusion in those patients in whom disruption of iliac veins or the inferior vena cava is a possibility. A catheter *should be placed in the bladder in all patients*. Those who have decreased skin perfusion with resultant pallor and coolness, narrow pulse pressure, tachycardia, and orthostatic hypotension, are likely to have lost in excess of 20 to 25 per cent of their blood volume. Cardiac output will have decreased in approximate proportion to blood loss. Deterioration of mental status indicates a more severe loss of blood volume, usually in excess of 40 per cent. Fluid resuscitation should be started, it is useful to sequentially number each new bag of fluid. Blood volume should be restored to at least a level at which a central venous pressure of several mm Hg is obtained. If crystalloid is used for this purpose, 3 or more liters may be required if the previously described signs are present. If a pneumatic suit ("G" or "MAST" suit) has been inflated around the victim's abdomen and lower limbs, a variable but potentially large amount of intravascular volume may have been shifted centrally.[7,8] The measured central venous pressure will then not be an accurate reflection of total intravascular volume. The suit should be deflated one compartment at a time, with careful observation of hemodynamic status, when volume replacement has started *and* when immediate surgery can be performed if necessary.

Premedication Agents

These should not be used routinely. Extreme caution is necessary in hypovolemic patients, and agents without effective antidotes should be avoided. Although narcotics are effective in relieving pain and anxiety, they dilate peripheral blood

vessels and may produce further hypotension with resultant cerebral ischemia adding to the sedative effect of the narcotic, causing regurgitation of gastric contents and aspiration. Cimetidine, 300 mg intramuscularly, is sometimes advocated as a means of decreasing gastric acidity in emergency surgery patients. This is not universal practice and we do not do this routinely.

OPERATING ROOM MANAGEMENT

Preparation of Equipment

In order to provide anesthetic care for major trauma at a moment's notice, a completely ready operating room should be available at all times. The anesthesiologist should have the following recently checked equipment in place: (1) anesthesia machine, 2. volume-controlled ventilator, with appropriate values preset, (3) suction, 4. laryngoscope with spare blades and endotracheal tubes with stylets, (5) appropriate drugs (pancuronium, succinylcholine, ketamine) drawn into labeled syringes, (6) two intravenous infusion sets with pumps and blood warmers, prefilled with crystalloid solution, 7) material required for placement of arterial lines, (8) warming blanket and/or a device to provide heated humidified inspired gases, (9) defibrillator with internal and external paddles, 10) calibrated equipment to monitor electrocardiograph, arterial blood pressure, central venous pressure, neuromuscular blockade, and temperature.

Choice of Anesthetic (Regional or General)

We prefer general anesthesia to regional for the more major injuries, particularly in the presence of an unstable cardiovascular status or injuries of the abdomen or thorax. Spinal anesthesia does not permit control of ventilation and the resultant sympathetic block prevents an important homeostatic response to hypovolemia. In patients with abdominal injuries, the extent of the necessary exploration and procedures is usually uncertain preoperatively, which precludes limited block levels. On the other hand, infiltration anesthesia or regional blocks can be extremely useful for the management of the more minor peripheral injuries, provided that attention is paid to the maximum safe dose of the agent selected relative to the patient's body size and physical status.

Induction and Maintenance of General Anesthesia

During induction of anesthesia, aspiration of gastric contents into the lungs may follow passive regurgitation or active vomiting. The latter may be avoided by using a rapid intravenous induction sequence. When diaphragmatic relaxation occurs secondary to cerebral ischemia, heavy sedation, or anesthesia, passive regurgitation may occur as a result of the difference in pressure between the abdomen and the thorax. Several hours of delay in scheduling surgery may decrease the probability of food remaining in the stomach, but this is never totally reliable and may be contraindicated by the urgency of the injury. A low gastric acidity and/or an empty stomach cannot be assumed for extended periods following trauma. Therefore, the following steps should be taken:

1. In all cases of intestinal obstruction, ileus, or gastroduodenal perforation or bleeding, a nasogastric suction tube should be placed, and the stomach aspirated immediately prior to induction, although this does not ensure an empty stomach.
2. The probable ease of laryngoscope and oral intubation should be assessed.

5. With powerful suction available, anesthesia should be induced using a small dose of a nondepolarizing muscle relaxant (this may minimize an increase of intragastric pressure when succinylcholine is subsequently administered[91]), preoxygenation for at least three minutes of quiet breathing or four or five maximum inspirations, then anteroposterior pressure applied over the cricoid cartilage (compressing the upper esophagus[92]), and a rapidly acting intravenous hypnotic and muscle relaxant (usually succinylcholine) administered intravenously.

Laryngoscopy, tracheal intubation, cuff inflation, and checks of tube location are carried out before cricoid pressure is removed. If laryngoscopy and intubation are expected to be difficult, other options are, in order of preference, intubation (nasally or orally) under topical anesthesia—if necessary with a fiberoptic bronchoscope—or a tracheotomy under local anesthesia. In many acute injuries of the jaw and neck, in which the state of the pharynx is in doubt, we prefer oral intubation under vision as a first step. Then, if nasal intubation is required, a nasal tube may be advanced under direct vision with the larynx in full view and the airway protected. This permits full evaluation of the injury prior to nasal intubation.

Whenever possible, hypovolemia should be corrected before the patient is transported to the operating room and anesthesia is induced. If correction is not possible because of the nature and extent of the injuries (that is, the rate of hemorrhage exceeds the ability to restore intravascular volume), it may be necessary to induce "anesthesia" in the hypovolemic patient. If the patient is unconscious or severely obtunded, intubation of the trachea should be accomplished without drugs or with neuromuscular blocking agents alone. If the patient is conscious despite being uncorrectably hypovolemic, other techniques are required.

For many years it was common practice to use an ultra-rapidly acting thiobarbiturate such as thiopental for inducing anesthesia in this circumstance, frequently resulting in acute decompensation (including death) in an already severely hypotensive patient.[26, 28] These clinical observations may be attributed to the myocardial depression and decreased peripheral venous tone caused by these agents.[25, 29] *Ketamine is a rapidly acting intravenous agent that in normovolemic, healthy patients and laboratory animals results in increased heart rate, systemic vascular resistance, blood pressure, and cardiac output.*[30–34] These are indirect effects caused by increased central sympathetic outflow and baroreceptor blockade and decreased vagal tone.[34–37] Very small doses of ketamine (0.35 to 0.7 mg per kg intravenously) are useful for inducing "anesthesia" in hypovolemic, hypotensive conscious patients. If a dose greater than that dictated by the clinical situation is used, the indirect stimulatory responses are not elicited, and ketamine's direct action of myocardial depression[38] may result in cardiovascular decompensation. Once intubated, the patient should be mechanically ventilated to free the anesthesiologist's hands. Evidence is lacking that either respiratory acidosis or alkalosis is beneficial during massive hypovolemia. We therefore attempt to maintain normocapnia, which has the added advantage of not confusing interpretation of acid-base status.

Following induction, only oxygen and neuromuscular blocking agents are administered until the hemodynamic situation is stabilized and systemic blood pressure rises to a mean of at least 50 torr. At that point cerebral perfusion should be adequate, and it is then appropriate to consider the administration of other agents. The goal is to provide analgesia or amnesia with minimal cardiovascular disturbance. Since the clinical situation is still in great flux and conditions may deteriorate, in principle, agents that are easily removed or whose actions are readily terminated should be used. Cyclopropane and ether are contraindicated because of the risk of explosion in a setting with a multiplicity of personnel and electrical equipment.

Furthermore, cyclopropane decreases survival time in shocked dogs.[7] Halothane, enflurane, or isoflurane may be cautiously added in very small concentrations (for example, halothane 0.4 per cent) to the background of 100 per cent oxygen and its cardiovascular effects observed. All the inhalation agents are direct myocardial depressants[8–10] and may result in significantly decreased myocardial performance and hypotension if added too rapidly or in too great a concentration. Recent data suggest that isoflurane and halothane may be superior in these circumstances when compared with enflurane.[11] The anesthetist must pay extremely close attention to the variable clinical situation and be prepared to cease administration of all inhalation agents should hypotension ensue.

Although nitrous oxide is a superior analgesic, it is frequently depressant in the hypotensive, hypovolemic patient. Since it must be used in relatively high concentrations, this adds to the potential for hypoxia because of decreased inspired oxygen concentration. Furthermore, nitrous oxide will increase the volume of any previously entrained pneumothorax and will increase bowel distention. Although narcotics have been used in such circumstances, two objections may be raised. Once given, they cannot be removed as can the inhalation agents. Second, the use of naloxone to reverse narcotic action may be only partially successful because of hypoperfusion at the sites of action and because of shorter duration of action of the antagonist than the agonist. Recent evidence that administration of naloxone is of benefit in nonanesthetized shocked animals suggests that endorphins, and thus perhaps narcotics, are detrimental in such circumstances.[12] We have not observed awareness of pain in any patient questioned postoperatively following this conservative approach to the use of *central nervous system* depressants.

In selecting a muscle relaxant for continued use during the procedure, d-tubocurarine is avoided because of its propensity to release histamine, resulting in further hypotension. Pancuronium is preferred to gallamine because of its greater vagolytic properties[13] and its lesser obligatory dependence on renal excretion.[14] Metocurine and NC 45 (not yet clinically available) have the least cardiovascular actions of *non depolarizing* muscle relaxants.

Hemodynamic Management

After securing the airway and establishing ventilation, hemodynamics remains the primary issue. Because of the rapidity and intensity of physiologic response to hemorrhage—increased sympathetic system activity, increased renin-angiotensin system activity, increased vasopressin, peripheral circulatory effects, acidic metabolites, direct hypoxic effects, and fluid shifts—and the multiplicity of therapeutic maneuvers in the acute situation, the hemodynamic status of the patient will change rapidly.

Accordingly, accurate beat-to-beat blood pressure monitoring is an important aspect of the acute management. For this reason and to allow repeated, rapid sampling of arterial blood for measurement of Po_2, Pco_2, and pH, an indwelling arterial cannula *should* be placed as *early in* the operating room sequence as feasible, if necessary by surgical cut-down, and connected to a pressure transducer for continuous measurement of blood pressure. The arterial line should be placed in the upper extremity because it may be necessary to cross clamp the thoracic aorta. A central venous (superior vena cava or right atrial) cannula should be placed, thus permitting, while the patient is in the emergency room or soon after arrival in the operating room. In the operating room, introduction through an internal jugular vein is favored

[illegible] preferable to an antecubital or subclavian vein, both because of the ease [illegible] of insertion through the former and the accessibility of this route while [illegible] proceeds. To permit continuous accurate assessment of central venous pres[illegible] [illegible] for [illegible] verification of position, the cannula should be connected to a pressure transducer. The preponderance of victims of major trauma are young and [illegible] heart disease; thus central venous pressure will usually be an adequate [illegible] of left-sided filling pressure. Placement of a pulmonary arterial line in [illegible] of the massively traumatized patient is neither necessary nor advisable; [illegible] better spent tending to higher priority issues.

If there is a need for assessment of intraoperative left-sided filling pressure, a [illegible] catheter may be inserted directly if thoracotomy has been performed. Direct observation of the degree of filling of the heart is also useful in the evaluation of the patient's volume status. The early stages of resuscitation of the massively bleeding patient require continuous communication between the surgeons and the anesthetists as to the nature and extent of the injuries and the hemodynamic indices. If it is necessary to cross-clamp the aorta to provide adequate blood flow to the brain and heart in the presence of massive hypovolemia, subsequent removal of the clamp may cause hypotension from circulating volume filling a previously empty, acidotic [illegible]. Consequently, reperfusion should be established gradually as he[illegible] [illegible] permit, with addition of volume or base, or both, as required.

Intraoperative Fluid Resuscitation. The amount of fluid volume to administer [illegible] the systemic blood pressure and the cardiac filling pressure. Fluids are [illegible] as rapidly as possible until the central venous pressure is in the normal [illegible] patient (8 to 10 torr) or the systemic blood pressure is in [illegible].

M[illegible] and discussion have surrounded the issue of which fluid to [illegible]. The [illegible] may currently choose from whole blood, packed cells, salt [illegible] [illegible] protein-containing fluids, colloids or other osmotically active [illegible] as dextran. Whole blood is the fluid of choice despite some deficiencies [illegible]. Whole blood offers the advantages of the ability to transport as [illegible] and off-load oxygen and carbon dioxide, contains most clotting factors [illegible] supply, and is a good buffer at physiologic pH. The disadvantages of [illegible] include: low storage temperature (4°C) with high thermal capacity, [illegible] clotting factors V, VIII, and possibly XI; lack of functional platelets after [illegible] storage; low pH; high potassium concentration; decreased red cell sur[illegible]; [illegible] of red cell membrane antigens, which requires typing and cross-[illegible] of the patient's blood with the blood to be transfused (although the U.S. A[illegible] had highly favorable experience in Viet Nam using unmatched low anti-A [illegible] titer group O[illegible] and the need for crossmatch has been questioned [illegible]); presence of citrate; risk of transmission of hepatitis; and decreased red [illegible] diphosphoglycerate (DPG) concentration, resulting in high hemoglobin af[illegible] for oxygen.

Blood banks are increasingly fractionating whole blood into its component parts, separating plasma from red cells. Consequently, we must often rely on packed red cells of [illegible] spun to hematocrit of approximately 70 per cent. To decrease vis[illegible] and [illegible] administration, packed cells should be reconstituted to an ap[illegible] normal hematocrit prior to transfusion. Sodium chloride (0.9 per cent) [illegible] fluid recommended by the American Association of Blood Banks for use [illegible] [illegible]. Because packed cells contain little plasma, some of the advantages

stored blood are diminished. Oxygen transport is not affected, however, and the CO_2 transport capability is only somewhat decreased as is buffering capacity and, of course, all clotting factors.

Despite considerable laboratory and clinical investigation, there is no firm evidence that the use of *microfilters for blood administration is beneficial.*[1] The resistance of these greatly impedes rapid blood administration, and we therefore do not recommend their use in this setting.

Note that when extremely rapid infusion of viscous fluids is required, there is considerable difference in resistance to flow between various types of infusion equipment and blood warmers. Stopcocks offer high resistance and therefore should not be used.

Incredibly, until the transfusion recipient's blood is typed, fluids other than blood must be administered. Current evidence indicates that in this regard colloid is of no advantage over crystalloid [illegible] and in fact, may be detrimental.[2-4] Given the expense of the former and the availability and ease of administration of the latter, there seems to be little, if any, reason to administer colloid in the acute resuscitative period. Resuscitative fluids undergoing research and development include fluorocarbons and stromal-free hemoglobin, either in solution or encased in lipid vesicles. The oxygen content of fluorocarbons is proportional to the partial pressure of oxygen in the fluid and reaches an acceptable level only at very high P_{O_2}. Furthermore, fluorocarbons are extremely expensive, with extraordinarily long half-lives.

Recently it has been possible to prepare hemoglobin with very little, if any, stromal elements, thus eliminating renal toxicity,[5] and offering the advantage of high oxygen content at normal P_{O_2}. Furthermore, hemoglobin so prepared can be stored for years in a lyophilized form at room temperature for prolonged periods of time, and since no red cell membranes and antigens are present, standard blood typing is unnecessary. Current research is focused on solving the problems of short intravascular half-life (two to four hours as a result of renal excretion) and low P_{50} (approximately 12 mm Hg) as a result of dissociation of hemoglobin monomers. Nevertheless, stromal-free hemoglobin has been shown to be superior to albumin in supporting myocardial function.[6] Should the problems of half-life and low P_{50} be resolved, stromal-free hemoglobin may find its place in the earliest phases of resuscitation of the massively bleeding patient.

Persistent Hypotension Despite Apparently Adequate Fluid Administration. This situation is observed at some stage in the operative or postoperative management of many patients who have sustained extremely traumatic injuries. The first checks should be of the accuracy of the monitoring system.

Transducers and manometers must be appropriately positioned, and it is useful to have placed a blood pressure cuff on the limb that has been cannulated for the arterial pressure. The occlusion pressure can then be used as a cross check. Possible causes of the continuing hypotension must then be reviewed. These include tamponade, hemorrhage, hemothorax, pneumothorax or pericardial tamponade, acidosis, hypothermia or cardiac arrhythmias, overventilation or anesthesia. Hypocalcemia may be present in extreme cases of hyperinfusion, hypothermia, and massive transfusion.

If correction of acidosis is ineffective in restoring systemic pressure, we empirically administer calcium chloride, 1 gm intravenously, since ionized calcium measurements are not readily available. Calcium and other pressors have diminished effectiveness during acidosis.

Myocardial failure in a previously healthy young trauma victim is not common without direct myocardial injury or prolonged myocardial hypoxia. However, if all other possible causes have been excluded or treated, additional fluids may be administered until the central venous pressure is 20 to 25 torr. If arterial pressure does not respond, pressor agents (dopamine or dobutamine, 3 to 12 μg per kg per minute intravenously initially) may be infused. An unusual cause of myocardial failure following perforating chest injuries is coronary air embolism,[76] which may be diagnosed by direct observation of the coronary arteries. The question of the existence of a "myocardial depressant factor" in shock is controversial.[24, 46, 56, 67] In addition to hemorrhage, metabolic acidosis and hypothermia are the two most common secondary aggravating factors in the massively bleeding traumatized patient.

Acid-Base Balance

Poor tissue perfusion results in accumulation of lactic acid because of decreased availability of oxygen at the end of the electron transport chain and decreased hepatic uptake of lactate during severe reductions of hepatic blood flow or during severe hypoxia.[7, 8] It is not clinically convenient to measure lactic acid. However, its appearance in the blood will result in a nearly stoichiometric increase in base deficit. Base deficit may be rapidly computed from measurements of arterial P_{CO_2} and pH.[37, 38, 39] Arterial blood gases and pH should be measured as soon as possible. The primary treatment of acidosis secondary to hypovolemia is obviously volume replacement. If volume is restored and perfusion pressure is satisfactory, the acidosis will be corrected as the liver takes up lactate and the tissues cease lactate production. Thus, treatment of acidosis per se will not be required. However, if hypotension persists, this may be partially due to acidosis. Ideally, the magnitude of this acidosis should be measured. If data are not yet available, it is safe to administer $NaHCO_3$ as a therapeutic test. It is unusual to observe clinically important cardiovascular effects of metabolic acidosis at base deficits less than 10 mEq per liter, and in this setting acidosis of considerably greater magnitude is common. Whole body base deficit is usually calculated from the formula 0.3 base excess (BE, mEq per liter) × body weight in kg. Thus, 200 or more mEq of $NaHCO_3$ may be required. Since the cardiovascular status is usually unstable when administration of $NaHCO_3$ is indicated, a calculated dose will not provide exact correction. Repeated evaluation is necessary. Based on recent evidence that, over a wide temperature range, vertebrate plasma pH is closely related to the pH of water and the ionization of imidazole,[5] P_{CO_2} and pH should be measured at 37 C and not corrected to the patient's temperature. In any event, over the clinical range, computation of base excess is very nearly independent of temperature.

It is not clear whether measured P_{O_2} should be corrected to the patient's temperature or reported at 37 C. However, temperature correction is necessary for computation of alveolar-arterial difference in oxygen tension ($AaDO_2$). Furthermore, in the hypothermic patient, if temperature correction results in error it is on the side of patient safety.

Hypothermia

Poor perfusion, opening of major body cavities, and administration of fluids of temperature less than body temperature inevitably result in hypothermia. Hypothermia presents multiple dangers. Myocardial function decreases with temperature. In the clinical setting of decreased myocardial preload and prolonged poor myocardial perfusion, myocardial hypothermia is poorly tolerated. As myocardial temper-

above falls to approximately 30°C., arrhythmias become common, with refractory ventricular fibrillation occurring within a further decrease of 1 to 3 centigrade degrees. Hypothermia adds to the coagulation defects by causing sequestration of platelets.[1] This phenomenon is *reversible with rewarming*. Additional problems of hypothermia include alteration of drug action and half-life and confusion of interpretation of blood gas, pH, and acid-base data.

Temperature should be measured continuously by a thermistor or thermocouple placed in the esophagus, just behind the heart, or by use of the thermistor on a thermodilution pulmonary artery catheter, if one has been inserted. These sites are preferred because blood and myocardial temperature are of prime concern, and as blood and myocardial temperature change, temperature will change more slowly at other sites such as the rectum.[2]

In the massively bleeding traumatized patient it is possible to prevent severe hypothermia, although it is not possible to maintain normothermic conditions. All intravenous fluids should be warmed during administration. Commercially available devices can effectively warm blood while producing minimal resistance, thus allowing for high flow rates.[3, 4] A plugged-in connected warming blanket should always be in place on the operating table. The device should be set and switched on at 40°C. *at first notice of a patient's* likely transport to the operating room, since these devices require 10 to 20 minutes to reach operating temperature. These blankets, although useful, are not "less than optimal value because of poor peripheral circulation during massive hypovolemia. Accordingly, heated inspired humidity may be of value in preventing serious hypothermia, since nearly *all the right atrial output will* be exposed "at a thin layer to the inspired heat in the pulmonary circulation. If the foregoing measures fail, warm crystalloid solution should be placed in the chest or abdominal cavities.

Coagulation

A bleeding diathesis following massive blood loss and replacement is not uncommon. Causes are lesions of banked blood, hypothermia, consumption coagulopathy, and platelet dysfunction. Coagulation factors V, VIII, and possibly XI have storage half-lives of approximately one week. Fortunately, only 5 to 30 per cent of normally present quantities of these factors are necessary for surgical hemostasis. Furthermore, the liver can rapidly produce large quantities of factor VIII once circulation has been restored.[5] Platelet function is severely impaired within minutes of storage at 4°C., with survival limited to less than 48 hours.[6] Many blood banks remove platelets from blood after its collection. Thus, nearly all blood transfused is free of *functional platelets*, creating a dilutional thrombocytopenia.[7] Furthermore, hypothermia causes platelet sequestration.[1] Fresh frozen plasma contains all coagulation factors except platelets. The role of fresh frozen plasma or fresh (less than 24 hours old) whole blood is controversial.[2, 8, 9, 10, 11]

The coagulopathy of massive transfusion occurs commonly when between one and two times the estimated blood volume has been administered. Ten units of platelets should be administered if further significant transfusion is anticipated or generalized oozing is apparent. Most hospital blood banks do not stock platelets, which thus must be ordered well in advance. Additional units of platelets will be required if hemorrhage is not controlled. Although this is controversial, we also administer 2 units of fresh frozen plasma after 10 units of blood or packed cells and additional 2 for each further 5 units of transfused blood.

Development of a consumptive coagulopathy (possibly resulting from release of tissue thromboplastins) will further deplete the diluted platelets and already decreased clotting factors.

The most convenient method for determining the etiology of a bleeding disorder in the victim of major trauma is to observe the coagulation time. If, in a glass tube, a good clot does not form or does so only after a prolonged period of time, decreased clotting factors are implicated. If the clot forms but does not retract, thrombocytopenia is the likely cause. If the clot lyses, *fibrinolysis is likely*.

Calcium is bound by citrate in banked blood, but its clinical importance as a cause of the bleeding diathesis[1] of massive transfusion and of decreased myocardial function[2,3] is controversial. We do not administer calcium routinely as prophylaxis against coagulation defects.

SPECIAL PROBLEMS

Thoracic Injuries

Three problems may require special actions by the anesthesiologist.

Pulmonary Injuries. Systemic air embolism due to pressure in the alveoli exceeding pressures in adjoining perforated pulmonary vessels is not uncommon.[4] Occasionally, a massive bronchial air leak may prevent effective mechanical ventilation. Placement of a double lumen endotracheal tube provides maximal control of this problem and prevents hemorrhage into the dependent lung during lateral thoracotomy. If this technique is not possible, a long endotracheal tube capable of being advanced into a main bronchus should be used. Inhaled agents should include only oxygen and anesthetic vapor until measurements of pulmonary oxygen exchange are obtained.

Aortic Injuries. Prolonged supra-renal clamping of the aorta may cause renal and spinal cord ischemia. *The higher the clamp, the greater the likelihood of* resultant left ventricular failure from the great increase in afterload. If control below the aortic injury is feasible, a shunt may be placed during the period of clamp-off. Restoration of volume will then prevent the aforementioned problems. However, if distal control is not feasible and a shunt is not placed, an agent such as sodium nitroprusside may be required to permit volume loading while the aortic clamp is in place.[5] Arterial pressure monitoring should be from the right arm if the injury may be *to the arch of the aorta*. *If time permits*, left ventricular filling pressure should be monitored.

Cardiac Injuries and Tamponade. Rapid surgical correction is essential. Anesthesia is induced with a small dose of ketamine (0.35 to 0.7 mg per kg), which usually maintains cardiac function, rather than sodium thiopental, which depresses venous return and myocardial contractility. Although the maintenance of a high cardiac filling pressure is theoretically important and intravenous fluid should be given to achieve it, this is only a short-term, temporizing measure.

Spinal Injuries

The approach to securing an airway has already been discussed. Although use of succinylcholine is contraindicated several days after a denervation injury, there is no evidence of muscle membrane instability in the first few hours. Thus, if otherwise indicated, succinylcholine may be used. Patients in halo traction requiring

anesthesia for other injuries are intubated nasally under topical anesthesia if necessary using a fiberoptic bronchoscope. Acute spinal cord injuries, particularly in the cervical or high thoracic regions, result in a "spinal shock" syndrome. Large volumes of intravenous fluid may be required to maintain adequate cardiac filling pressure and systemic pressure. Central venous pressure should be monitored, and α-adrenergic agents may be used to compensate for the sympathetic denervation, provided that cardiac filling pressures and urine output are maintained.

Head Injuries

Intracranial pressure is decreased as much as possible by administration of mannitol or furosemide, induction of hypocapnia ($Paco_2 \leq 30$), and maintenance of a low venous pressure. A mechanical ventilator wave-form with rapid inspiratory flow rates may assist in minimizing intrathoracic pressure. To minimize autonomic response to intubation and incision, barbiturates and narcotics, because of their less unfavorable effects on intracranial pressure, are probably preferable to the anesthetic vapors. However, there is no strong evidence to support large dose barbiturate therapy for brain protection in this setting.

Intraoperative Complications. Marked hypotension immediately following intracranial decompression is common. This should be managed with fluids and, if necessary, the judicious use of a pressor such as ephedrine. We routinely establish arterial and central venous pressure monitoring as soon after induction as possible. A coagulopathy is occasionally seen. The etiology of this disseminated intravascular coagulation–like picture is not clear, but fresh blood or fresh frozen plasma, or a combination of the two, is the therapy of choice. Neurogenic pulmonary edema may be seen rarely, and facilities must be available for intraoperative application of positive end-expiratory pressure.

The Open Globe

Facial injuries may include trauma to the globe of the eye. Loss of vitreous humor, iris, and lens may result in permanent blindness and require evisceration. To minimize this possibility, every effort is made to avoid raising intraocular pressure. The factors that control intraocular pressure are similar to those affecting intracranial pressure. Induction of anesthesia must be smooth and there must be no "squeeze" of eye muscles or straining during surgery. The fasciculations that accompany administration of succinylcholine cause a transient increase in intraocular pressure, but its importance or the effectiveness of a previously administered non-depolarizing agent in the open eye is uncertain. Our preference includes the use of "precurarization," a large dose of thiopental, and succinylcholine; or, if a smaller dose of thiopental would be safer, substituting a large dose of pancuronium (0.15 mg/kg) for the succinylcholine. Either way, the profound myoneural block is monitored and monitored with a nerve stimulator. The ventilator is adjusted to avoid hypocapnia.

THE IMMEDIATE POSTOPERATIVE PERIOD

At the end of surgery, for all but the most massive trauma when hypovolemia has been corrected and the hemodynamic status is stable, the temperature is greater than 34°C, and pulmonary gas exchange is satisfactory, it is usually appropriate to extubate the patient and to administer oxygen in the recovery room. Because of the

danger of possible regurgitation and aspiration of gastric contents, the patient should not be extubated until he or she is awake and has intact upper airway reflexes.

After major trauma, many patients remain unstable in a number of ways, including blood volume and hemodynamics, temperature, acid-base balance, and coagulation. In some instances, pulmonary edema is present as a result of pulmonary trauma or secondary to previous cardiac ischemia or massive fluid load. Intracranial pressure may require monitoring. Intensive care will be necessary, but the process of transfer is not simple. There will be a lapse of time before the patient is settled in the intensive care unit (ICU) with all monitoring systems functioning and the ICU staff conversant with the ongoing problems. There are various ways to meet this situation, but the guiding principles are as follows:

1. Establish and maintain as much monitored stability as is feasible in the operating room; that is, do not take a "blind leap" to the ICU with a hypovolemic, hypotensive patient whose blood gas levels and acid-base status are unknown. If necessary, stay in the operating room long enough to correct these defects.

2. Use portable electronic monitoring and mechanical ventilation equipment for the move to the ICU and insure that these are functioning well before leaving the operating room. In patients with severely impaired cardiorespiratory status, a change to manual ventilation may result in a sufficient change in intrathoracic pressure to cause increased hypotension or intracranial pressure, or to permit a change in lung volume with resulting deterioration in oxygen exchange.

3. Forewarn the ICU to prepare the necessary ventilation and monitoring equipment and any other urgently required therapy, such as blood products.

4. On arrival, establish continuity of blood pressure monitoring and ventilation as a first priority. Stay with the patient until all monitoring and support systems are reestablished and the ICU staff is familiarized with the patient's circumstances and orders.

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Title: KETAMINE INCREASES CATECHOLS, BUT CAUSES CARDIOVASCULAR DEPRESSION AND ACIDOSIS IN HYPOVOLEMIC SWINE

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Introduction. Hemorrhage stimulates the sympathoadrenal system. Although anesthetic agents may cause further stimulation, it is not clear that this would be beneficial when inducing anesthesia during hypovolemia. Ketamine, like cyclopropane before it, has been recommended because, during normovolemia, it causes cardiovascular stimulation. Idvall(1) and Longnecker and Sturgill(2) concluded that rats, bled during ketamine anesthesia, had better redistribution of blood flow than rats bled during pentobarbital or halothane anesthesia. However, Theye et al and we have observed detrimental metabolic effects in dogs bled during cyclopropane(3) or ketamine(4) anesthesia in comparison with halothane, isoflurane, or enflurane.

These studies examined the effects of bleeding after the animal was anesthetized. We sought to test the hypothesis that in awake animals, compensation for hemorrhage would be detrimentally influenced by an anesthetic agent which, during normovolemia, causes cardiovascular stimulation.

Methods. Thirteen domestic swine (19.5±0.6kg; mean±SEM) were anesthetized with halothane in O_2 to allow insertion of peripheral venous and systemic and pulmonary arterial cannulae. Each pig was intubated, paralyzed with metocurine (0.2mg/kg, supplemented as needed), and mechanically ventilated to maintain $PaCO_2$ during all conditions at 40 torr. PaO_2 was always maintained at 150-210 torr. Administration of halothane was discontinued and each pig was studied supine, normovolemic, after the end-tidal halothane concentration (measured by mass spectrometry) had decreased to less than 0.50 torr. Measurements were repeated after a blood volume reduction of 30% over 30 minutes. Each pig was randomly assigned to one of two groups: Group I, control, no anesthetic; or Group II, induction of anesthesia with ketamine, 6.6±0.5 mg/kg, iv. The dose given to each pig was one-half the minimal induction dose determined while normovolemic, 24-48h before the experiment. Group II was studied again 5 minutes after induction of anesthesia; Group I was studied at a comparable time. Student's unpaired t-test was used to compare the awake normovolemic state with the awake hypovolemic state and to compare Group I with Group II after induction of anesthesia.

Results. 30% blood loss decreased right and left heart filling pressures, mean systemic blood pressure, and cardiac output. Systemic vascular resistance, lactate concentration and plasma catecholamines increased; O_2 consumption did not change (table I). Before induction of anesthesia there were no differences between Groups I and II. Although ketamine, in comparison with the control group, caused a pronounced increase in plasma catecholamines 5 minutes after induction of anesthesia, mean systemic blood pressure, cardiac output, and systemic vascular resistance decreased. O_2 consumption decreased while lactate concentration increased (table II).

Conclusion. We have found that, in hypovolemic swine, induction of anesthesia with ketamine: a) causes a further increase in plasma catecholamines, b) causes cardiovascular depression, and c) results in failure to meet total-body O_2 demand. We conclude that during hypovolemia either a) additional cardiovascular response to further sympathetic stimulation is not possible or b) that such stimulation is overwhelmed by the direct depressant effects of ketamine.

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TABLE I

RESPONSE TO 30% BLOOD VOLUME LOSS IN AWAKE SWINE

	Normovolemic	Hypovolemic	P
$\overline{BP}a$ (torr)	132±1	101±2	<0.001
Q_t (ml/kg/min)	181±2	118±2	<0.001
SVR (torr/l/min)	37.5±0.4	45.6±0.9	<0.05
Lactate (mmol/l)	0.94±0.02	1.50±0.08	<0.05
$\dot{V}_{O_2}$ (mlO_2/kg/min)	7.4±1.0	8.1±0.1	NS
Epinephrine (pg/ml)	239±7	1018±105	<0.025
Norepinephrine (pg/ml)	214±15	399±21	<0.05

Data are mean±SEM, n = 13, except for catechols, n = 9

$\overline{BP}a$: mean systemic blood pressure, Q_t: cardiac output, SVR: systemic vascular resistance; $\dot{V}_{O_2}$ oxygen consumption.

TABLE II

RESPONSE 5 MINUTES AFTER ANESTHETIC INDUCTION

	Control (Group I)	Ketamine (Group II)	P
$\overline{BP}a$	103±4	42±2	<0.001
Q_t	119±3	74±3 (5)	<0.005
SVR	44±2	30±2 (5)	<0.05
Δ Lactate[a]	-0.01±0.02	+0.34±0.05 (5)	<0.025
Δ $\dot{V}_{O_2}$[a]	+1.0±0.2	-1.5±0.1	<0.005
Epinephrine	340±45 (4)	4643±196 (4)	<0.001
Norepinephrine	305±59 (4)	1122±123 (4)	<0.025

Data are mean±SEM in Group I: 7 swine and Group II: 6 swine, except as noted in parenthesis.

a) Change from awake, hypovolemic value
Abbreviations and units same as in Table I.

Acid-base curve and alignment nomograms for swine blood

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WEISKOPF, RICHARD B., MARY I. TOWNSLEY, KATHRYN K. RIORDAN, DALE HARRIS, AND KAREN CHADWICK. *Acid-base curve and alignment nomograms for swine blood.* J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 54(4): 978–983, 1983.—To construct acid-base curves and alignment nomograms for swine blood, we added known amounts of acid or base to aliquots of swine blood with three different concentrations of hemoglobin. Pairs of blood samples were equilibrated at two different CO_2 partial pressures, and blood pH was measured. Data were analyzed by computer, and mean values were created for complete data of four swine. Curve and alignment nomograms were constructed by computer. The resultant nomograms for swine blood differ from those constructed by Siggaard-Andersen for human blood, most importantly at base-excess values of +10 to +25 mmol/l. The possible reasons for the observed differences are discussed and, although not completely resolved, may be related in large measure to the accuracy of pH determination and the methodology of nomogram construction.

carbon dioxide partial pressure; blood pH; computer analysis

RECENTLY THE PIG has become increasingly popular as an experimental animal. To maintain "normal" values during some of our experiments (9), we needed to know the acid-base parameters of swine blood. We were unable to find this information in the literature. Although we lacked information indicating specific differences in acid-base parameters between human and experimental animal blood, we were not especially concerned until the report of Scott Emuakpor et al. (12), which indicated differences between human and canine blood in the hemoglobin-independent plot of log CO_2 partial pressure (P_{CO_2}) vs. pH. Those findings and our need to characterize the acid-base status of swine blood led to the present investigations. As a result, acid-base curve and alignment nomograms were constructed for swine blood, and the methodology used for their construction was reappraised.

METHODS

Collection and handling of blood. Four studies were performed; the blood of a different pig was used in each study. Each pig's blood was handled in a similar fashion. Pigs were anesthetized with thiopental, and 330 ml of arterial blood were collected in heparin (33 units/ml blood). Whole blood was centrifuged, and three red blood cell dilutions (to packed cell volumes of approx 9, 27, and 45%) were prepared from the separated red blood cells and plasma. A sample of well-mixed original whole blood and samples of each dilution were placed in ice for later determination of total protein (6), hemoglobin (6), 2,3-diphosphoglycerate (8), and methemoglobin (3) concentration. Blood samples were prepared in duplicate at base excesses (BE) of −25, −20, −15, −10, −5, 0, +5, +10, +15, and +20 meq/l at each of three hemoglobin concentrations (a total of 60 samples) by adding 100 μl of working acid or base solution (see below) to 3.9 ml of blood. To prevent red cell lysis, blood samples were briefly centrifuged at low speed, and the acid or base solution was added to the swirling supernatant plasma. Samples were then gently but thoroughly mixed. Blood preparation was followed by tonometry and measurement of pH. One member of each pair of blood samples was equilibrated for 7 min in an Instrumentation Laboratories model 213 tonometer with a gas mixture of 2.72% CO_2 in O_2; the other member of the pair was similarly equilibrated with a gas mixture of 9.60% CO_2 in O_2. The gas mixtures had been previously analyzed in triplicate by the method of Scholander (11). (When these gas flows and concentrations and blood volumes were used in preliminary experiments, equilibration of blood with CO_2 was achieved within 4–5 min.)

We measured pH using a Severinghaus-UC electrode (13) thermostatically controlled at 38.8°C and a Lorenz model 3 DBM-3 amplifier. The pH electrode was calibrated with precision reference buffers (pH 6.839 and 7.379 at 38.8°C; Radiometer 3-ml sealed glass ampules). Electrode calibration was checked with the 7.379 buffer before and after each blood sample reading. Measurements were performed in duplicate with a maximal allowable difference between the two determinations of 0.003 pH units. The mean (±SD) of the difference between the paired reading for all samples, calculated without respect to sign, was 0.001 ± 0.001 pH units. Measurements of pH were corrected for red cell suspension effect (17, 18). P_{CO_2} was measured in duplicate by using a CO_2 electrode (Radiometer E5036) in a steel-and-glass cuvette (Radiometer D616) thermostatically controlled at 38.8°C. The electrode was calibrated with gas mixtures analyzed in triplicate by the method of Scholander (11). A reading of

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a standard gas with a P_{CO_2} close to that expected for the blood sample was taken before and after each blood sample reading. Blood CO_2 tensions were systematically measured to ensure equilibration of blood with CO_2. Mean (±SD) difference between measured and expected blood P_{CO_2} (calculated without regard to sign) was 0.88 ± 0.27 Torr at P_{CO_2} of 67.9 Torr. Readings for pH and P_{CO_2} were corrected for electrode drift.

Preparation and standardization of acid and base solutions. A 1.0 N solution of Na_2CO_3 (100%, certified alkalimetric standard, Fischer Scientific) was prepared and used to standardize, by titration, what we determined to be a stock solution of 1.01 N HCl. The 1.01 N HCl was used as a titrant for a stock solution of what we determined to be 1.03 N $NaHCO_3$. Concentrations of 0.2, 0.4, 0.6, and 0.8 N acid and base working solutions were prepared volumetrically from the stock solutions. All working solutions were titrated as described above. All titrations were repeated after completion of the bench laboratory work reported here; no differences were noted between determinations made before and after these experiments.

Data analysis. The data generated for each pig resulted in three sets of values (1 for each concentration of hemoglobin). Each set contained values for pH and P_{CO_2} for blood samples at each BE (0–20 meq/l of acid or base added). However, since the BE of the blood drawn from the animal was not necessarily zero, the data were "normalized" to correct for any small acid-base imbalance at the time of sampling. To accomplish this, Siggaard-Andersen and Engel (19, 22) plotted constant CO_2 titration curves (pH vs. acid or base added) at both CO_2 tensions for each hemoglobin concentration. They curve fit their data by eye and by hand and similarly shifted the axis for the added acid or base so that zero corresponded to pH 7.400 for the P_{CO_2} 40-Torr curve (O. Siggaard-Andersen, personal communication; see Fig. 4). In following their methodology, we noticed that minor differences in curve fitting and shifting the data "by eye" resulted in relatively large differences in the final nomograms. Unable to arbitrarily resolve these observed differences, we used precise mathematical and graphical techniques that were implemented by a computer.

For each concentration of hemoglobin, we calculated regression coefficients by using a forward stepwise (with a backward glance) selection procedure (5) to fit the model

$$\begin{aligned} pH = (C_1 + C_2{*}BE + C_3{*}BE^2 + C_4{*}BE^3 \\ + C_5{*}BE^4){*}\log P_{CO_2} + C_6 + C_7{*}BE \\ + C_8{*}BE^2 + C_9BE^3 + C_{10}{*}BE^4 \end{aligned}$$

This model has the following properties: *1*) for any given BE the relationship between pH and log P_{CO_2} is linear; *2*) the slope and intercept of this relationship may vary nonlinearly with BE; and *3*) for each concentration of hemoglobin the calculated coefficients define a model that fits the data with high statistical significance ($R^2 > 0.99$).

For each level of hemoglobin, the equation was "*normalized*" *to a pH of 7.400 for a BE of zero and a* P_{CO_2} of 40.0 Torr, based on the observations of Orr et al., in six awake chronically catheterized swine (10). These investigators measured arterial CO_2 partial pressure (Pa_{CO_2}) as 38 Torr and arterial pH (pH_a) as 7.43 (BE < 1 mmol/l). This seemed sufficiently close to the human standard of P_{CO_2} of 40 Torr and pH of 7.40 to retain these values for BE = 0 for the purpose of nomogram construction. This normalization was accomplished by solving each derived regression for BE at pH 7.4 and P_{CO_2} 40 Torr using the Jenkins-Traub three-stage algorithm (7). The result, BE_{error}, represented the deviation of the acid-base status of the animal from zero at the time the blood was drawn. Values for the amount of acid or base added (BE) were then adjusted (shifted) by the amount of BE_{error}. The above regression model was then refit with the shifted BE values.

Curve nomogram. By using the equations resulting from the above curve-fitting procedure, we calculated the relationship between pH and log P_{CO_2} for each of the three concentrations of hemoglobin at each level of BE. Siggaard-Andersen and Engel (22) stated that for each level of BE, there exist a single pH and P_{CO_2} that are independent of hemoglobin concentration. Therefore for each level of BE the three lines calculated above should intersect at a single point. Brodda (2) has calculated that this can occur only if shifts in water between the red blood cell and plasma that result from changes in pH are taken into account. Experimentally the three isohemoglobin lines at each level of BE result in three intersections. Several approaches are possible when approximating the hemoglobin-independent point by computer. For example, the three points of intersection could be averaged. However, this method can be shown to be subject to large error when two of the hemoglobin lines are nearly parallel. Other simple methods of approximation are similarly subject to error. At the expense of being more complex and cumbersome, our approach avoided this potential error.

We approximated the hemoglobin-independent point by calculating the point that minimized the mean square difference in pH and log P_{CO_2} between the point and the three buffer slope (isohemoglobin) lines. Intuitively such a point would be that requiring the smallest change in the projection of the three hemoglobin lines to produce a common intersection. We derived this point in the following fashion.

Let (pH_{ind}, log $P_{CO_{2\,ind}}$) be the Hb-independent point, and let m_i and b_i ($i = 1, 2, 3$) be the slopes and intercepts of the three linear relationships calculated from the regression model for a given BE (i.e., $pH = m_i \log P_{CO_2} + b_i$). Solve the following set of equations for pH_{ind} and log $P_{CO_{2\,ind}}$

$$\frac{dX}{d(pH_{ind})} = 0$$

where $X = (pH_1 - pH_{ind})^2 + (pH_2 - pH_{ind})^2 + (pH_3 - pH_{ind})^2$

$$\frac{dY}{d(\log P_{CO_{2\,ind}})} = 0$$

where $Y = (\log P_{CO_2} - \log P_{CO_{2\,ind}})^2 + (\log P_{CO_2} - \log P_{CO_{2\,ind}})^2 + (\log P_{CO_2} - \log P_{CO_{2\,ind}})^2$

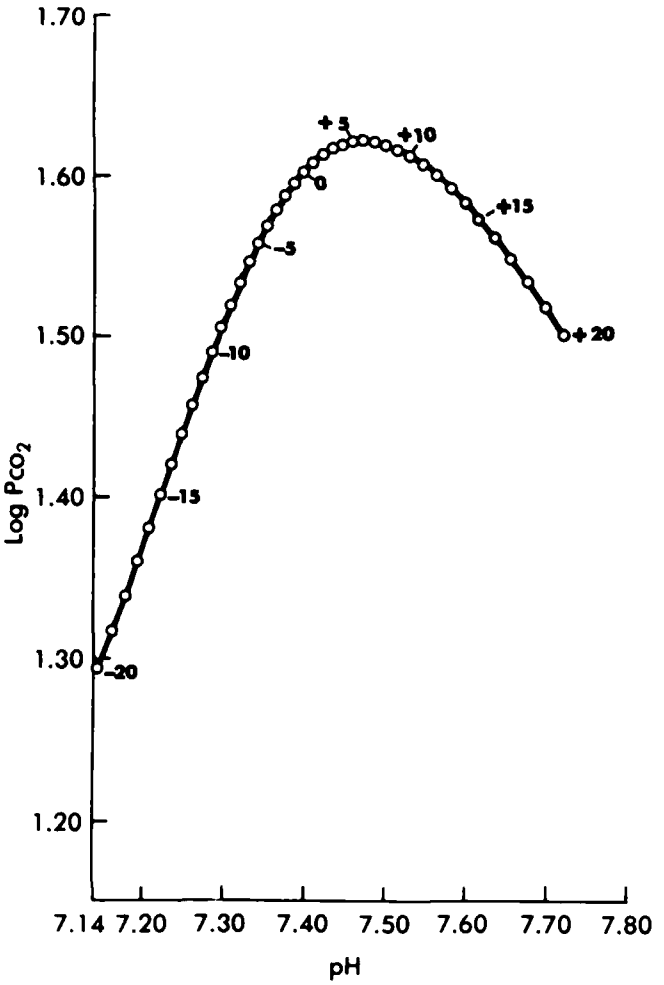

FIG. 1. Mean acid-base curve nomogram for swine. See text for derivation of "mean" values for 4 swine and construction of nomogram.

TABLE 1. *Swine base-excess curve nomogram*

Base Excess, meq·l^{-1}	Coordinates		Base Excess, meq·l^{-1}	Coordinates	
	pH, units	P_{CO_2}, Torr		pH, units	P_{CO_2}, Torr
−20	7.145	19.7	0	7.400	40.0
−19	7.162	20.7	1	7.412	40.6
−18	7.178	21.8	2	7.424	41.0
−17	7.194	22.9	3	7.436	41.4
−16	7.208	24.1	4	7.448	41.6
−15	7.223	25.2	5	7.461	41.8
−14	7.236	26.3	6	7.474	41.8
−13	7.249	27.5	7	7.488	41.8
−12	7.262	28.6	8	7.502	41.6
−11	7.275	29.8	9	7.517	41.3
−10	7.287	30.9	10	7.532	40.9
−9	7.298	32.0	11	7.548	40.4
−8	7.310	33.1	12	7.565	39.8
−7	7.321	34.1	13	7.582	39.1
−6	7.333	35.1	14	7.600	38.3
−5	7.344	36.1	15	7.618	37.4
−4	4.355	37.0	16	7.637	36.4
−3	7.366	37.9	17	7.657	35.3
−2	7.377	38.6	18	7.678	34.2
−1	7.389	39.4	19	7.700	33.0
			20	7.722	31.7

P_{CO_2}, CO_2 partial pressure.

$$\left.\begin{aligned} pH_i &= m_i \log P_{CO_{2\,ind}} + b_i \\ \log P_{CO_{2_i}} &= \frac{pH_{ind} - b_i}{m_i} \end{aligned}\right\} \text{ for } i = 1, 2, 3$$

A curve nomogram was then plotted by connecting the hemoglobin-independent points for a series of BE values.

Alignment nomogram. Curve-shifted data were used for a computerized construction of the alignment nomogram, in a manner similar to that described by Siggaard-Andersen (20).

Mean Values

For each pig the previously derived regression equations (1 for each concentration of hemoglobin) were used to calculate pH values at each standard P_{CO_2}, at each standard BE. The resulting four pH values (1 per pig) at each P_{CO_2}, BE, and concentration of hemoglobin were averaged, thus producing a set of data representing the "mean" pig. Raw data could not be used for this purpose, because the BE values of the sampled blood differed slightly among pigs, thus requiring differing degrees of curve shifting to achieve normalization. Mean data were

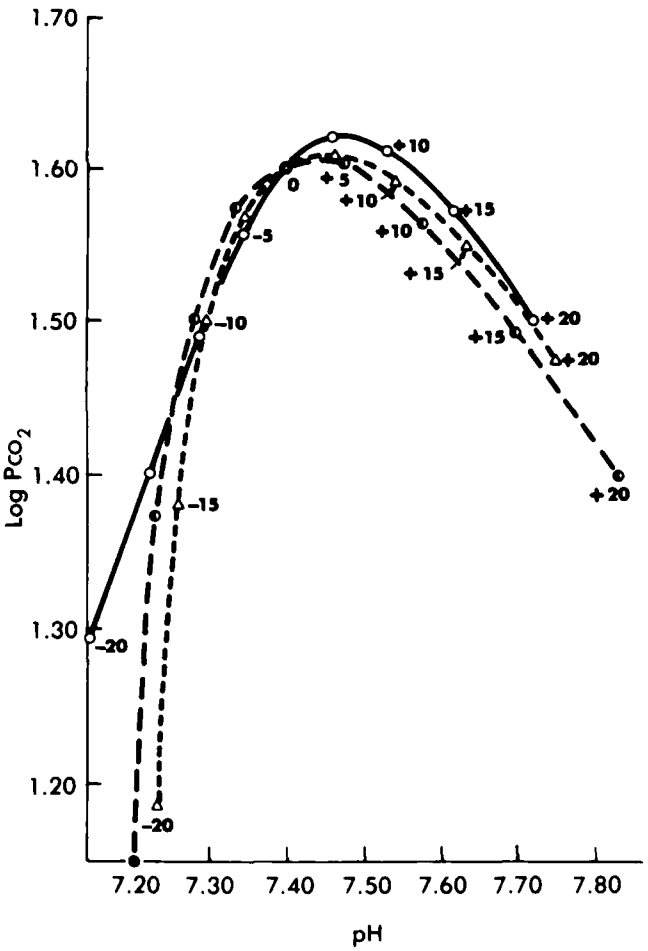

FIG. 2. Comparison of our "mean" data for swine (○– – –○) with Siggaard-Andersen's data for humans (△– – –△) and Scott Emuakpor's data for canines (◐– – –◐).

then handled as if they were from a single pig, and the above-described analysis was performed. The result was separate mean curve and alignment nomograms.

RESULTS

The mean acid-base curve nomogram for swine blood is depicted in Fig. 1; the data are presented in Table 1. We compared our curve nomogram for swine blood with that of Siggaard-Andersen (19) for human blood and with that of Scott Emuakpor (12) for canine blood (Fig. 2). The alignment nomogram is shown in Fig. 3.

DISCUSSION

Our mean curve and alignment nomograms for swine blood are different from nomograms for human (19, 20) and canine blood (12) (Fig. 3). As a technical check, we

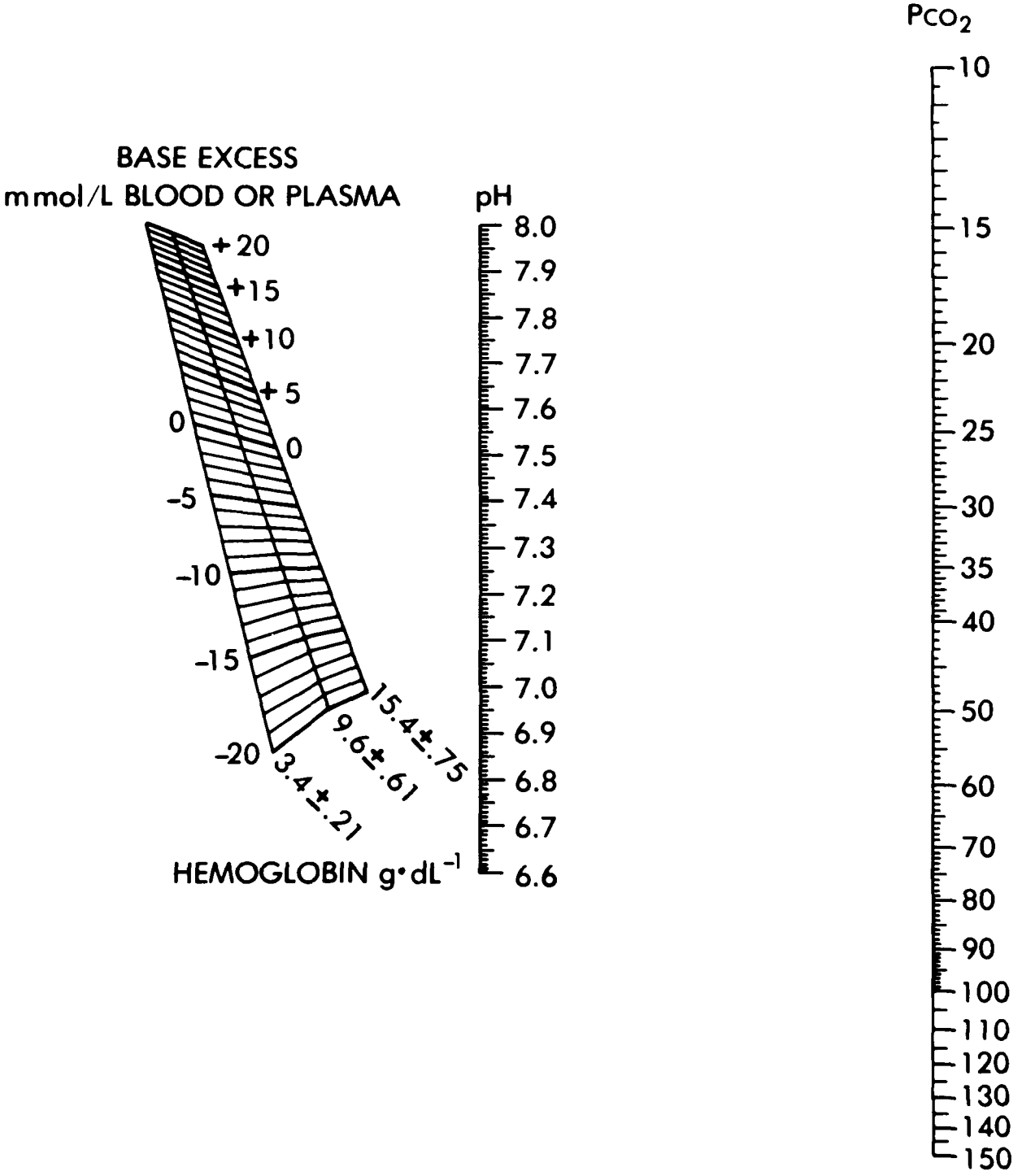

FIG. 3. Mean acid-base alignment nomogram for swine. See text for derivation of "mean" data and construction of nomogram.

performed similar but limited experiments with blood of two human volunteers. The resultant limited nomograms (30 data points, at hemoglobin concentrations of 3, 10, and 15 g/dl) were similar to that of Siggaard-Andersen (20) between BE of −10 and +10 mmol/l ($P > 0.5$) but different from our swine nomogram ($P < 0.001$). To compare the swine alignment nomogram with that drawn by Siggaard-Andersen for human blood (20), we plotted our data of known pH, P_{CO_2}, hemoglobin concentration, and BE on the Siggaard-Andersen alignment nomogram as if we were unaware of the true BE value. The BE values determined from the Siggaard-Andersen nomogram were compared with the true BE values. The resultant estimated BE differed ($P < 0.001$) from the known BE of all blood samples at all concentrations of hemoglobin and BE, except at a BE of zero, for which the results are definitionally identical. In nearly all cases, however, the calculated value was within ±10% of the true value.

There are several possible explanations for the differences between our nomogram and that of Siggaard-Andersen. Neither set of data is based on the blood of a large population: Siggaard-Andersen used the blood of four humans, we used four swine. However, in our experiments, individual variation did not appear to be an important problem.

Some of the observed differences may relate to differences in species. Scott Emuakpor et al. (12) described a curve nomogram for canine blood that differed from Siggaard-Andersen's curve nomogram for human blood. The buffer value of plasma proteins and hemoglobin can vary among mammalian species (4, 23), and this may account for some, but not all (21), of the differences among the nomograms. Measured total protein of our swine blood (7.2 ± 0.3 g/dl) was similar to the normal value for humans.

To create blood samples of altered BE, we avoided important dilution of plasma proteins by adding small amounts of relatively concentrated (0.2–0.8 N) acid or base. We thereby produced some alterations in ionic strength of blood, which may account for some of the differences between our nomograms for swine blood and those of Siggaard-Andersen for human blood (19, 20). However, our curve nomogram for swine blood differs even more from the original curve nomogram of Siggaard-Andersen and Engel for human blood (22), for which the identical method of addition of acid or base was used.

To construct the nomograms, we followed the general methodology of Siggaard-Andersen. However, the two methodologies differ in several important ways.

We used a method different from that of Siggaard-Andersen to "shift" the original data to normalize the drawn blood to the established definition of BE = 0, pH 7.400, P_{CO_2} 40.0 Torr. Siggaard-Andersen (personal communication) accomplished the following tasks graphically, fitting the curve and selecting the points by eye: *1*) curve fitting the two constant CO_2 titration curve plots (pH vs. acid or base added) at each concentration of hemoglobin; 2) estimating similar data for P_{CO_2} 40 Torr, assuming a linear relationship between log P_{CO_2} and pH, followed by curve fitting of the P_{CO_2} 40-Torr data as in *1*; 3) estimating the axis shift (acid or base added) to align the P_{CO_2} 40-Torr data so that at a pH of 7.400, BE was set equal to zero; and *4*) estimating from the hand-drawn iso-P_{CO_2} curves the pH at preselected levels of BE. An example of this graphic process, using data from one of our swine, is shown in Fig. 4. We accomplished all the above with a computer, the resulting curve-fit equations describing the data with an accuracy of more than 99.95%.

To draw the BE grid, Siggaard-Andersen used his previously developed pH-log P_{CO_2} curve nomogram for one set of blood pH and P_{CO_2} values and an empirical relationship between buffer base, hemoglobin concentration, and BE to estimate the required second pair of blood pH and P_{CO_2} values. Because of our uncertainties regarding the specificity of the pH-log P_{CO_2} curve nomogram and the empirical relationship described above, we chose to use our original data and the computer-generated curve fits to that data to determine the BE grid.

To generate the continuous isohemoglobin lines of the BE grid from the original data, we developed computer-

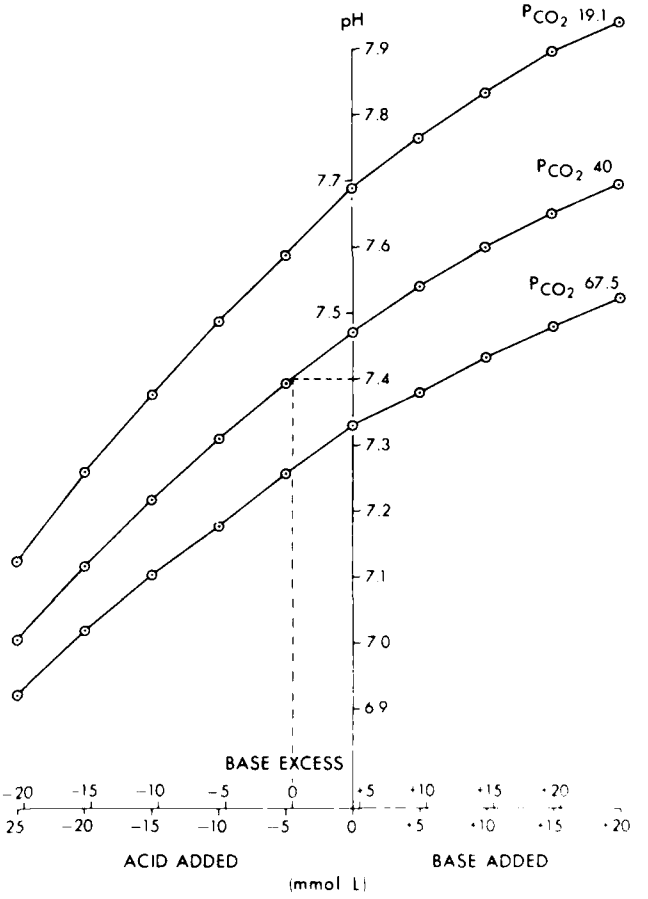

FIG. 4. Base-excess (BE) "normalization" by graphically "curve shifting" data. Example (using data for 1 of our swine) of graphic solution of *1*) curve fitting 2 constant CO_2 titration curves, 2) estimating similar data for P_{CO_2} 40 Torr, 3) estimating axis shift to align P_{CO_2} 40-Torr curve to pH 7.400 at BE = 0, and 4) estimating pH at preselected values of BE. On *horizontal axis* lower values indicate known amounts of acid or base added, upper values indicate resultant BE after axis shifting. See text for additional details. We accomplished these tasks by computer, not graphically.

ized empirical mathematical equations that were plotted by computer. Siggaard-Andersen used points determined graphically to draw curves by hand. Although we have not examined systematically the differences between the two techniques, we did note before completion of the computer programs that seemingly small, unimportant interpretive differences that occurred when drawing curves by hand through the original data created relatively large differences in the estimated amount required to shift the "acid-or-base-added" axis. These differences created relatively large differences in the alignment nomogram.

Another difference between Siggaard-Andersen's nomogram and our own is the temperature at which tonometry and measurement of pH were performed. Siggaard-Andersen's experiments were performed at 38°C; ours were performed at 38.8°C (normal body temperature for swine). Siggaard-Andersen correctly stated that measurements performed at temperatures within ± 2°C of 38°C (the standard temperature of his nomogram) are "without any practically significant error" (20). We temperature corrected some of our pH and P_{CO_2} data from 38.8 to 38.0°C and then estimated BE from our nomogram. All estimates were within ±0.1 mmol/l of the true value. Similarly, using established data for pK' solubility of CO_2 in plasma (14), we determined that change in calculated plasma HCO_3^- between 38.0 and 38.8°C was less than 0.1 mmol/l.

Finally there are differences in the methodology of measuring pH, the major variable on which these nomograms rest. As a result of advances in design and construction of pH electrode (13) and amplifier (16), our determinations of pH probably had less variability [0.001 ± 0.001 (SD) pH units] than did the measurements of Siggaard-Andersen. Variations in the measurement of pH that are usually considered minor (e.g., 0.003 pH units) result in surprisingly large differences in the final nomogram, because relatively small changes in the slope of nearly parallel lines greatly alter their point of intersection. Small variations in pH create the largest changes in the nomogram in the BE range of +10 to +25 meq/l, the range in which our nomogram differs most from that of Siggaard-Andersen.

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CARDIOVASCULAR AND METABOLIC SEQUELAE OF INDUCING ANESTHESIA WITH KETAMINE OR THIOPENTAL IN HYPOVOLEMIC SWINE

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(Key words: Anesthetics, intravenous: ketamine; thiopental. Blood: loss; volume. Blood pressure: drug effects; measurement; peripheral vascular resistance. Heart: cardiac output; vascular pressures; ventricles. Hemorrhage.)

ABSTRACT

If further sympathetic stimulation is neither possible nor desirable during moderate hypovolemia, anesthetic agents capable of sympathetic stimulation would not be advantageous for induction of anesthesia during hypovolemia. To test this hypothesis, 21 swine were studied during normovolemia and after 30% of their estimated blood volume was removed. Swine were randomly divided into three equal groups to receive no anesthetic or the minimal anesthetic dose of ketamine (6.65 ± 0.38 mg/kg, iv) or thiopental (5.77 ± 0.21 mg/kg, iv). After the initial response to hypovolemia, animals given no drug did not exhibit further changes during the hypovolemic period. Five minutes after induction of anesthesia in the hypovolemic state, ketamine but not thiopental caused large increases in plasma epinephrine, norepinephrine, and renin activity. Despite these differences, both anesthetics equally depressed systemic vascular resistance, mean systemic arterial blood pressure, heart rate, and cardiac output. Ketamine, but not thiopental, decreased stroke volume. Neither anesthetic affected oxygen consumption. Both anesthetics caused similar increases in blood lactate concentration. Thirty minutes after induction of anesthesia, plasma epinephrine, norepinephrine, and renin activity remained higher in animals given ketamine than in those given thiopental. Stroke volume, systemic vascular resistance, cardiac output and oxygen consumption did not differ among groups; however, only the animals given ketamine showed further increase in blood lactate concentration and base-deficit. Thirty minutes after infusion of shed blood, cardiac output and blood lactate concentration were greater in the animals given ketamine than in those given thiopental or no anesthetic. Ninety minutes after infusion of shed blood, no differences existed among groups. We conclude that after moderate hemorrhage, further increase in circulating catecholamines is possible, but that the levels achieved either exceed the maximal effective concentration at site(s) of action or their effects are overwhelmed by the depressant effects of ketamine. This study failed to document any advantage of ketamine over thiopental when used in the minimal anesthetic dosage for induction of anesthesia during hypovolemia.

INTRODUCTION

Although hypovolemia is usually corrected before induction of anesthesia, some conditions may not permit restoration of blood volume before surgical intervention. Thus, it is occasionally necessary to induce anesthesia in a hypovolemic patient.

Compensation for hemorrhage is complex; important mechanisms include stimulation of baroreceptors and sympathetic and renin-angiotensin systems, and increases in heart rate and systemic vascular resistance. It is not known to what extent anesthetics modify these mechanisms during a stimulated state of compensation for blood loss. Because of its pressor action, cyclopropane was once the recommended anesthetic agent for hypovolemic patients. However, laboratory studies subsequently demonstrated poorer survival rates for animals bled while anesthetized with cyclopropane than while anesthetized with other drugs.[1] Ketamine, like cyclopropane, has been advocated for use during hypovolemia[2-4] because of the hypertension and tachycardia produced in normovolemic animals[5] and humans[6,7]. Studies of animals bled during ketamine anesthesia produced differing interpretations as to the usefulness of this drug during hypovolemia.[8-11] Likewise, the use of thiopental for induction of anesthesia during hypovolemia is controversial.[12]

Neither ketamine nor thiopental has been studied in a controlled fashion for induction of anesthesia during hypovolemia. The single laboratory reports of administration of ketamine[13] or thiopental[14] to hypovolemic dogs are insufficiently described and without adequate controls. We conducted this study to examine the influence of anesthetic agents on compensatory mechanisms

to hemorrhage in awake animals, and to test our previously stated hypothesis[8] that sympathetic stimulation may be neither possible nor beneficial during induction of anesthesia in hypovolemic subjects.

METHODS AND MATERIALS

We briefly anesthetized 21 young swine (Chester-White-Yorkshire crossbreed; weight 20.0 $\pm$ 0.25 kg, mean $\pm$ SE) with halothane in oxygen and nitrogen, which was adjusted to maintain arterial oxygen tension at 150-200 mmHg). The animals were paralyzed with succinylcholine, 2 mg/kg iv (later followed by administration of metocurine, 0.2 mg/kg iv, which was supplemented as required). The trachea was intubated, and the animal ventilated (tidal volume, 20 ml/kg; frequency was adjusted to maintain P_aCO_2 at 39.9 $\pm$ 0.2 mmHg). After local infiltration with 0.25% bupivacaine, catheters were placed through the superficial femoral artery into the abdominal aorta and percutaneously through the innominate vein into the pulmonary artery.

Halothane was then discontinued and eliminated by ventilation until its end-tidal concentration, as measured by mass spectroscopy (Perkin Elmer Model MGA 1100AB), fell to less than 0.5 mmHg (0.05 MAC). We waited an additional 30 min before beginning our studies. The animals remained intubated and mechanically ventilated.

Systemic arterial, pulmonary arterial, and right atrial pressures were transduced (Statham 23Db), and mean pressures derived electrically by a Gould preamplifier. Cardiac output was estimated using a thermodilution technique (3 ml, 0° C, 0.9% NaCl), a thermistor-tipped 5-Fr pulmonary arterial catheter (Edwards Laboratories) and an analog computer (Edwards Model 9520A). The temperature of the injectate was measured continuously. Cardiac output was measured until two successive values produced satisfactory logarithmic washout curves and differed by no more than 0.2 l/min. We continuously measured

partial pressures of oxygen, carbon dioxide, and halothane at the orifice of the endotracheal tube using mass spectroscopy. These physiologic variables were recorded by a Gould polygraph (Model 2800). Temperature, measured in pulmonary arterial blood, was maintained within 0.5° C of its initial value using circulating water heating pads.

We calculated systemic vascular resistance (SVR) as the difference between mean systemic arterial (BPa) and right atrial pressures, divided by cardiac output. Pulmonary vascular resistance was calculated as the difference between mean pulmonary arterial and pulmonary arterial wedge pressures, divided by cardiac output.

During each experimental condition, we used Radiometer electrodes in steel-and-glass cuvets to determine partial pressures of oxygen and carbon dioxide, and a Severinghaus-UC electrode to measure pH, in both systemic and pulmonary arterial blood. All electrodes were maintained at 37° C. Calibrating gases and buffers were measured before and after each blood sample reading; the measurements were corrected for electrode drift, liquid-gas factor, and body temperature. Oxygen concentrations in systemic and pulmonary arterial blood were measured in duplicate by a galvanic cell instrument (Lex-O_2-Con-TL, Lexington Instruments). We calculated oxygen consumption as the product of cardiac output and the difference between arterial and mixed venous oxygen concentrations. Base-excess was estimated using a nomogram for swine blood.[15]

During each experimental condition, arterial blood samples were obtained for enzymatic measurement of whole-blood lactate concentrations[16] and plasma

epinephrine and norepinephrine concentrations,[17] and for radioimmunoassay of plasma renin activity[18].

All of these measurements and calculations were made while animals were normovolemic. Then 33% of each animal's blood volume (estimated using equations developed by Engelhardt[19]) was removed through the arterial cannula during a 30-min period. An additional 30 min was allowed before measurements were made for this hypovolemic state. Each animal was randomly assigned to receive ketamine (Group K), thiopental (Group T), or no anesthetic (Group C). In all other respects, animals were treated similarly.

We determined the appropriate dose of drug for each animal as follows. Forty-eight to seventy-two hours before the day of experiment, a cannula was inserted into an ear vein of each (unmedicated) swine. Thiopental or ketamine, 6 mg/kg iv, was given rapidly, followed by repeated iv injections of 2 mg/kg every 15-20 s until the animal no longer responded to a painful ear stimulus. On the day of experiment, one-half this dosage was administered as a single bolus. In a separate set of subsequent experiments on swine, using eight littermates, we established that 30% hypovolemia reduces the anesthetic requirement by approximately 33% for thiopental and approximately 40% for ketamine. (Weiskopf RB and Bogetz MS, unpublished data). These reductions did not differ significantly from each other. Group K received ketamine, 6.65 $\pm$ 0.38 mg/kg; and Group T, thiopental, 5.77 $\pm$ 0.21 mg/kg.

All measurements were repeated 5 and 30 min after induction of anesthesia. Shed blood was then returned to the animal and measurements were repeated 30 and 90 min later.

For each experimental condition, results among groups were compared using analysis of variance with repeated measures and the Newman-Keuls method of multiple comparisons.[20] Statistical significance was accepted when $P < 0.05$.

RESULTS

Hemorrhage (Table 1)

Right- and left-sided cardiac filling pressures decreased. Plasma renin activity, plasma concentrations of epinephrine and norepinephrine, heart rate, and systemic vascular resistance increased. However, these responses did not sustain stroke volume, cardiac output, or mean systemic arterial blood pressure. Oxygen consumption increased; and a decrease in base-excess and an increase in whole-blood lactate concentration indicated the development of systemic acidosis.

Induction of Anesthesia with Ketamine or Thiopental, and Comparable Period in Non-anesthetized Animals (Table 2).

Control Animals: After the initial changes caused by hemorrhage, no variable further changed in control animals during the hypovolemic period.

Five Minutes after Induction of Anesthesia: Five minutes after administration of ketamine ($P < 0.05$), but not thiopental ($P > 0.05$), plasma epinephrine, norepinephrine, and renin activity had increased. Despite these differences in circulating vasoactive agents, ketamine and thiopental produced similar changes in compensatory cardiovascular responses to hemorrhage. Systemic vascular resistance was less in Groups K and T than in Group C. Neither agent changed right- or left-sided cardiac filling pressures. Although ketamine and thiopental significantly decreased heart rate, the resulting rates did not differ significantly from the rate for Group C.

Although only ketamine decreased stroke volume (0.95±0.12 to 0.70±0.10 ml/kg, $P<0.005$), the resulting values did not differ among groups. Cardiac output decreased similarly in Groups K and T to values less than that for Group C. As a result, mean systemic blood pressures did not differ between Groups K and T; however, both groups had pressures that were less than those for Group C. Oxygen consumption did not differ among the groups, but whole-blood lactate concentrations increased similarly in Groups K and T.

Thirty Minutes after Induction: Thirty minutes after induction, most values had recovered towards preanesthetic levels during hypovolemia; however, significant differences remained. Plasma epinephrine concentration was still greater in Group K than in Groups C and T (which were not different from each other). Although plasma norepinephrine concentration was greater in Group K than in Group T, these two groups did not differ from Group C. Plasma renin activity was greater in Group K than in Group T, but the activity in these groups was not different from Group C. For Groups K and T, SVR did not differ from each other, but was less than that for Group C.

Right- and left-sided cardiac filling pressures and heart rate remained similar, and cardiac output no longer differed among groups. Also, the resultant mean systemic arterial pressure was similar for Groups T and K; both were less than that for Group C.

Oxygen consumption did not differ among groups, but whole-blood lactate concentration continued to increase and base-excess continued to decrease significantly only in Group K ($P < 0.05$).

Return of Shed Blood: Thirty minutes after return of shed blood, cardiac output was greater in Group K than in Groups C or T. Blood lactate was still greater in Group K than in either Group T or C. There were no other significant differences among groups.

Ninety minutes after return of shed blood, there were no significant differences among groups for any variable.

All animals survived 24 h, at which time they were killed.

DISCUSSION

The cardiovascular effects produced by induction of anesthesia with ketamine during hypovolemia differ from those seen during normovolemia. Heart rate, mean systemic blood pressure, and cardiac output increase when ketamine is administered to normovolemic animals[5] or man[6,7]. In contrast, these variables decrease during hypovolemia. In our study ketamine and thiopental produced identical cardiovascular changes initially. Although these two anesthetics affected plasma catecholamine concentrations and renin activity differently, both caused similar deterioration of the animal's compensation for hemorrhage, and decreased SVR, cardiac output, and BPa. Thirty minutes after induction, hypovolemic animals who had received ketamine for induction became progressively more acidotic, while those who had received thiopental or no anesthetic did not.

Administration of ketamine further increased circulating catecholamine concentrations above the already elevated levels caused by the sympathetic response to hypovolemia. Thus, one portion of our hypothesis was not supported. In swine, the sympathetic response to 30% hemorrhage was not maximal; further sympathetic response was possible. The concomitant increase in plasma renin activity after administration of ketamine may be a function of increased sympathetic activity,[21,22] other circulating substances,[21] or a separate action of ketamine. The progressive lactic acidosis 30 min after induction, seen only in the ketamine group, may be a result of increased oxygen demand caused by increased sympathetic activity without concomitantly increased blood flow, or decreased hepatic uptake of lactate, or both.

In intact experimental animals, it is not certain which measure best reflects inadequacy of tissue perfusion. Huckabee proposed blood "excess lactate" as a measure[23], but later Cain demonstrated blood lactate concentration to be at least as good[24], if not a better measure[25] of oxygen deficit. Previously, we have shown in asplenic dogs, bled while anesthetized, that blood lactate concentration and base-deficit developed to a greater extent when they were anesthetized with ketamine than with halothane, enflurane, or isoflurane[8]. Conversely, Longnecker et al. have reported higher excess lactate in rats bled while anesthetized with halothane than similar rats anesthetized with ketamine[11]. However, we have calculated that those rats anesthetized with ketamine had a greater base-deficit (approximately 11 mmol/l) than those anesthetized with halothane (approximately 2.5 mmol/l).

In these experiments, despite the increase in catecholamine concentrations and renin activity, SVR, BPa, and cardiac output decreased. This failure of massively increased levels of circulating catecholamines to maintain BPa, SVR, and cardiac output implies that ketamine has a powerful opposing depressant effect, or that the maximal response to stimulation had been achieved. Ketamine has been shown to be a direct myocardial depressant,[5,26-28] not to cause contraction of rabbit aortic strips,[29] and to relax phenylephrine-induced contracted rabbit aortic strips[29]. Similarly, thiopental depresses the myocardium[30] and peripheral vasculature.[31] In our experiments, both anesthetics decreased SVR. The fall in stroke volume index at a time when left ventricular preload increased, seen after administration of ketamine, tends to indicate myocardial depression. However, since heart rate, afterload, and myocardial compliance were not controlled, no conclusion

can be drawn.

Alternatively, the increase in circulating catecholamines in the animals given ketamine could have been a response to the hypotension produced by the drug. This would imply that thiopental blocked a similar response. Our experimental data can not differentiate between these proposed mechanisms. Nevertheless, our data do support the second part of our hypothesis: that further sympathetic stimulation during induction of anesthesia during hypovolemia is not beneficial.

Several aspects of our methodology should be discussed. Our animals were not "trained"; therefore, data obtained in the absence of anesthesia, with the animals' tracheas intubated and the animals mechanically ventilated, may not be equivalent to data for "resting" animals. Nevertheless, cardiovascular data we obtained for the unmedicated, normovolemic state fall within the range of values reported by other investigators.[19,32-39] Furthermore, hypovolemic and/or traumatized humans are not in a "resting" state. The few limited reports of hemorrhage in unmedicated swine have shown an arterial blood pressure response similar to that of our animals.[32,34,**] Because detailed cardiovascular response of unmedicated swine to hemorrhage has not been reported, we cannot compare some of our results with those of other

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**Hannon JP, Jennings PB, Dixon RS: Physiologic aspects of porcine hemorrhage. III. Heart rate and arterial pressure changes during spontaneous recovery from 30 and 50 percent blood volume loss in the conscious animal. Institute report no. 95, Letterman Army Institute of Research, Presidio of San Francisco, California.

investigators.

Hemorrhage produced changes similar to those we have observed in a larger group of similar swine (Weiskopf RB, Bogetz MS: unpublished data). All cardiovascular and metabolic responses to hemorrhage in our swine are consistent with what is known for man. Although the dog has been the species most frequently used to study hemorrhage, its response and that of the rat differ in important ways from that of man.[40,41] In these species, contraction of the hepatic sphincter causes splanchnic engorgement and a number of sequelae not seen in man.[40,41] The response of the gastrointestinal tract of swine in shock resembles that of man.[42]

Because we did not conduct a dose-response study, we cannot address the question of whether other doses of ketamine or thiopental could have produced different effects during hypovolemia. However, the minimal anesthetic dose required during normovolemia was determined for both agents and individually for each animal. This dose was then reduced by half, which is in close agreement with our subsequent findings that hypovolemia similarly reduces the anesthetic requirement for thiopental and ketamine. Smaller doses would not have been anesthetic, and other cardiovascular responses could have occurred.

Our data do not demonstrate a beneficial effect from using ketamine during hypovolemia. Studies reporting satisfactory use of ketamine for patients in "hemorrhagic shock" have had some shortcomings: the concomitant use of other drugs; and/or the failure to substantiate major blood volume deficit, to indicate the dose of ketamine administered, or to document cardiovascular responses at specific time intervals.[2-4] The literature concerning the use of thiopental for induction of anesthesia during

hypovolemia is also anecdotal.[12]

Our data indicate that moderate hypovolemia does not produce a maximal increase in circulating catecholamines. Administration of ketamine, but not thiopental, causes a further increase. However, the increased plasma concentrations do not further stimulate the circulation, either because they are above the maximal possible effective concentrations, or because their effect is overwhelmed by the depressant qualities of ketamine, or both. Administering ketamine for induction of anesthesia during hypovolemia did not offer any advantages over thiopental when both were used at the minimal anesthetic dose. The clinician should note that an anesthetic agent is not a substitute for adequate restoration of blood volume and venous return; and when an anesthetic must be administered during significant hypovolemia, cardiovascular depression should be expected.

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Table 1. Response of Swine to 30% Blood Loss

	Normovolemic	Hypovolemic	P
Mean right atrial pressure (mmHg)	1.3 ± 0.4	-0.6 ± 0.3	<0.001
PWP (mmHg)	2.8 ± 0.2	0.2 ± 0.3	<0.001
Plasma renin activity ($ng \cdot ml^{-1} \cdot h^{-1}$)	2.8 ± 0.5	8.2 ± 1.7	<0.005
Plasma epinephrine (pg/ml)	215 ± 21	776 ± 157	<0.005
Plasma norepinephrine (pg/ml)	216 ± 30	347 ± 66	<0.02
Heart rate (beats/min)	102 ± 5	145 ± 11	<0.001
Stroke volume (ml/kg)	1.77 ± 0.07	0.88 ± 0.08	<0.001
Cardiac output ($ml \cdot min^{-1} \cdot kg^{-1}$)	174 ± 5	113 ± 6	<0.001
BPa (mmHg)	129 ± 3	100 ± 6	<0.001
PAP (mmHg)	13.4 ± 0.5	9.4 ± 0.5	<0.001
Oxygen consumption ($ml\ O_2 \cdot min^{-1} \cdot kg^{-1}$)	7.27 ± 0.26	7.94 ± 0.28	<0.02
Base excess (mmol/l)	5.7 ± 0.6	3.3 ± 0.6	<0.01
Blood lactate (mmol/l)	1.10 ± 0.13	1.69 ± 0.25	<0.05
SVR ($mmHg \cdot l^{-1} \cdot min$)	37.3 ± 1.1	45.2 ± 2.3	<0.005
PVR ($mmHg.l^{-1}.min$)	3.05 ± 0.14	4.18 ± 0.21	<0.001

Values are means ± SE; n = 21.

PWP, pulmonary arterial wedge pressure; BPa, mean systemic arterial blood pressure; PAP, mean pulmonary arterial blood pressure; SVR, systemic vascular resistance; and PVR, pulmonary vascular resistance.

Table 2. Response of Swine to Induction of Anesthesia

	5 min after induction			
	No anesthetic	Ketamine	Thiopental	Statist. interpret.
RAP (mmHg)	-0.3 ± 0.8	-1.2 ± 0.7	0.2 ± 0.2	ns
PWP (mmHg)	0.0 ± 0.4	0.1 ± 0.6	1.9 ± 1.0	ns
Renin activity ($ng \cdot ml^{-1} \cdot h^{-1}$)	6.8 ± 2.8	28.7 ± 5.2	8.9 ± 4.3	K>T,C
Epinephrine (pg/ml)	285 ± 70	2657 ± 987	690 ± 310	K>T,C
Norepinephrine (pg/ml)	209 ± 62	660 ± 220	287 ± 170	K>T,C
Heart rate (beats/min)	162 ± 24	113 ± 11	116 ± 19	ns
Stroke volume (ml/kg)	0.79 ± 0.11	0.76 ± 0.10	0.74 ± 0.14	ns
Cardiac output ($ml \cdot min^{-1} \cdot kg^{-1}$)	117.9 ± 8.9	76.9 ± 5.1	74.0 ± 5.9	C>K,T
BPa (mmHg)	97.2 ± 9.4	41.4 ± 3.5	52.1 ± 7.8	C>T,K
PAP (mmHg)	8.5 ± 0.7	6.7 ± 0.8	8.1 ± 0.6	ns
$\dot{V}_{O_2}$ ($ml\ O_2 \cdot min^{-1} \cdot kg^{-1}$)	7.84 ± 0.55	6.91 ± 0.44	6.80 ± 0.32	ns
Blood lactate (mmol/l)	1.43 ± 0.37	2.78 ± 0.39	2.12 ± 0.37	K T C
SVR ($mmHg \cdot l^{-1} \cdot min$)	42.3 ± 4.9	29.4 ± 2.9	33.3 ± 3.5	C>T,K
PVR ($mmHg \cdot l^{-1} \cdot min$)	3.67 ± 0.25	4.82 ± 0.38	3.91 ± 0.93	ns
ΔBE (mmol/l)	0.4 ± 0.5	-0.6 ± 0.5	-0.1 ± 0.5	ns
ΔLac (mmol/l)	-0.01 ± 0.06	0.55 ± 0.23	0.65 ± 0.24	C<K,T

ne to Induction of Anesthesia during 30% Hypovolemia

nduction		30 min after induction			
Thiopental	Statist. interpret.	No anesthetic	Ketamine	Thiopental	Statist. interpret.
0.2 ± 0.2	ns	-0.4 ± 0.7	-1.4 ± 0.5	0.4 ± 0.4	ns
1.0 ± 1.0	ns	0.2 ± 0.4	0.4 ± 0.6	0.9 ± 0.4	ns
6.9 ± 4.3	K>T,C	8.0 ± 2.6	17.7 ± 4.6	5.3 ± 2.2	$\overline{K}$ C $\overline{T}$
390 ± 310	K>T,C	534 ± 246	2139 ± 1612	453 ± 142	K>C,T
187 ± 170	K>T,C	459 ± 132	598 ± 367	191 ± 101	$\overline{K}$ C $\overline{T}$
115 ± 19	ns	164 ± 23	121 ± 12	121 ± 18	ns
.74 ± 0.14	ns	0.84 ± 0.13	1.01 ± 0.07	0.86 ± 0.09	ns
4.0 ± 5.9	C>K,T	123.5 ± 7.6	112.9 ± 9.0	100.8 ± 5.5	ns
7.1 ± 7.9	C>T,K	107.5 ± 7.4	79.7 ± 9.1	77.3 ± 10.9	C>T,K
9.1 ± 0.6	ns	9.9 ± 1.0	8.3 ± 1.0	9.6 ± 13	ns
.80 ± 0.30	ns	7.33 ± 0.33	7.40 ± 0.70	7.18 ± 0.26	ns
.12 ± 0.37	$\overline{K}$ T $\overline{C}$	1.42 ± 0.58	3.31 ± 0.45	2.11 ± 0.36	K>T,C
7.3 ± 3.5	C>T,K	45.2 ± 5.0	36.3 ± 4.6	36.6 ± 3.9	C>T,K
.91 ± 0.93	ns	4.05 ± 0.55	3.57 ± 0.30	4.26 ± 0.40	ns
.1 ± 0.5	ns	0.2 ± 0.5	-1.5 ± 0.7	0.1 ± 0.6	C,T>K
.05 ± 0.04	C<K,T	0.00 ± 0.04	0.53 ± 0.17	-0.01 ± 0.16	T,C<K

Table 2 (continued)--Footnotes:

Values are means ± SE; n = 7 per group.
Group C, no anesthetic; Group K, ketamine; Group T, thiopental.
RAP, mean right atrial pressure; PWP, pulmonary arterial wedge pressure; BPa, pulmonary arterial blood pressure; $\dot{V}_{O_2}$, oxygen consumption; SVR, systemic vascular
ΔBE, change in base excess from previous state; ΔLac, change in blood lactate conce
$\overline{K}$ C $\overline{T}$ means that K is not statistically different from C, nor is C different f

; T, thiopental.
arterial wedge pressure; BPa, mean systemic arterial blood pressure; PAP, mean

mption; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance;

, change in blood lactate concentration from previous state.

nt from C, nor is C different from T, but that K is statistically different from T.

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11. Personnel Receiving Support for This Contract

1. Weiskopf, Richard B., M.D.: Principal investigator
2. Montgomery, Sue: Staff Research Associate
3. DeManincor, Darlene: Staff Research Associate

12. Addenda

A. Problems

During the contract year the following problems were encountered:

1. At different times, both SRA's (technicians) were hospitalized for unanticipated surgery; one was out for three weeks, the other for two months. During these periods the pace of research was slowed.

2. Overall progression of contract goals was slower than anticipated because of the need to conduct unanticipated studies for the purpose of scientific validation.

3. The mass spectrometer required repair (total down-time of three weeks) by the manufacturer (Perkin-Elmer) and by the manufacturer of the vacuum pump (Edwards Hi-vacuum). During this period it was not possible to conduct research.

4. The continuing problems we had with obtaining animals of consistent strain and size at a time when they were needed, came to a head during this past year. As a result, we were forced to seek a new vendor. Although the University provided us absolutely no help in this regard (and in fact the attitude at the Physiological Research Facility here at SFGH was one of obstructionism) with the help of the supply section at LAIR, we were able to locate a satisfactory vendor. Cost of the animals from the new vendor is similar to that which we were paying previously. The animals appear to be healthy, and of better temperament. Since this vendor is of some distance from San Francisco and delivery charges are added to all deliveries, we have attempted to buy swine in larger numbers for each delivery. This has added to our per diem costs. There was a period of transition between the two vendors where the flow of animals did not meet our needs.

B. Publications supported, copies of (pages not numbered for annual report).

13. Appendix

The following manuscripts and abstracts in preparation, follow.

1. Weiskopf RB, Bogetz MS: Hemorrhage reduces anesthetic requirement for ketamine and thiopental in swine

2. Weiskopf RB, Bogetz MS, Roizen MF: Nitrous oxide and halothane cause decreased cardiac output and lactic acidosis during hemorrhage

3. Bogetz MS, Weiskopf RB: Induction of anesthesia in swine during hypovolemia: comparison of halothane, enflurane, and isoflurane

Hemorrhage Reduces Anesthetic Requirement for Ketamine and Thiopental in Swine

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Abbreviated title: KETAMINE AND THIOPENTAL DURING HEMORRHAGE

(Key words: Anesthetics, intravenous: ketamine, thiopental. Blood, loss. Hemorrhage.)

ABSTRACT

The effects of moderate hypovolemia on the ansthetic requirements of ketamine and thiopental were evaluated in eight swine littermates during normovolemia and after 30% blood loss. Four animals received ketamine and four thiopental; and the minimal anesthetic doses of both drugs were determined. Each animal was studied on eight occasions. Moderate hypovolemia was found to decrease the anesthetic requirement of ketamine and thiopental significantly and similarly (thiopental, 33 $\pm$ 5%; ketamine 40 $\pm$ 5%).

INTRODUCTION

When anesthesia must be induced in a hypovolemic patient, a reduced dose of anesthetic agent is frequently used in an attempt to minimize adverse cardiovascular effects of the induction agent. It is not clear, however, whether the reduced dose produces anesthesia. Recently, Bogetz and Katz[1] described recall of awareness during surgery, by major trauma victims who were given a small dose or no anesthetic for "induction of anesthesia." Eger et al,[2] in three dogs, found that hemorrhage sufficient to reduce diastolic blood pressure by one-half to two-thirds decreased the minimal alveolar anesthetic concentration (MAC) of halothane by 20%. Such a decrease in MAC might be a consequence of impaired brain oxygenation resulting from decreased oxygen delivery. However, MAC also has been shown to decrease only when P_{aO_2} is below 40 torr;[3] and during severe isovolemic anemia, only when arterial oxygen content is below 5 vol %.[4] Other studies have combined use of other drugs with anesthetic agents, thus making unclear the effects of hemorrhage or hypotension alone on anesthetic requirement. Therefore, we investigated whether hemorrhage reduces the anesthetic requirement for two commonly used intravenous induction agents, ketamine and thiopental.

METHODS

Eight swine (Chester-White-Yorkshire cross) littermates (mean weight ± SE), 15.3 ± 0.4 kg) were divided into four pairs on the basis of similarity in weight. One of each pair was randomly assigned to receive thiopental (group T) or ketamine (group K). All animals were in good health for each study.

Animals were anesthetized four times while normovolemic, at least two days separating each study. Unmedicated animals were placed in a sling, and a cannula was inserted into an ear vein. In random order, on four separate occasions, group K animals were given ketamine 12.5, 15, 17.5, or 20 mg/kg. Group T animals were given thiopental 7.5, 10, 12.5, or 15 mg/kg. Eventually, each animal received all four doses.

Animals were anesthetized four times while hypovolemic, one week separating each study. Unmedicated animals were anesthetized briefly with halothane in oxygen and nitrogen while arterial and venous cannulae were inserted. Arterial blood samples were obtained; and PO_2, PCO_2, and pH measured by appropriate electrodes. Arterial blood pressure was transduced (Statham Model 23Db) and recorded (Gould Model 2800 polygraph). Halothane was discontinued, the animal allowed to awaken, and placed in a sling. Further experimentation was delayed until the end-tidal partial pressure of halothane, as measured by mass spectroscopy, fell to less than 0.5 torr (0.05 MAC). To prevent hypoxia during and after blood loss, animals were given 1-2 l/min oxygen by mask. Each animal was bled by 30% of its estimated blood volume[5] over a 30-min period. To ensure stability, 30 min of observation followed.

In random order, on four successive weeks, group K animals received one of four IV doses of ketamine: 2.5, 5, 7.5, or 10 mg/kg IV; group T animals received thiopental, 5, 7.5, 10, or 12.5 mg/kg IV. Eventually each animal again received all four doses.

Following the administration of each drug in either the normovolemic or hypovolemic state, the animal's response (i.e., movement or lack of movement) to a clamp on the tail was determined. Tail-clamp tests were performed 10, 20, 30, 45, 60, 90, 120, 180, 240, and 300 sec. after drug administration. These responses were analyzed statistically using the method of Waud.[6] In addition, the maximum dose of drug which failed to prevent movement in each individual animal and the minimum dose of drug which prevented the animal from moving was averaged for each animal. This average for the four animals in each group were compared between normovolemic and hypovolemic states by using student's t-test. Differences between the two states were compared for the two drugs, using student's t-test.

RESULTS

Hypovolemia reduced the minimum anesthetic dose for both thiopental ($P < 0.025$) and ketamine ($P < 0.01$) (Table 1). These reductions (thiopental 33% $\pm$ 5%; ketamine, 40% $\pm$ 5%) were not statistically different ($P > 0.2$) from each other. After hemorrhage and before drug administration, mean ($\pm$ SE) arterial blood gas values were as follows: PO_2, 177.8 $\pm$ 20.1 torr; PCO_2, 41.9 $\pm$ 1.5 torr; and pH, 7.323 $\pm$ 0.11. Mean ($\pm$ SE) arterial blood pressure was 92 $\pm$ 3 torr after hemorrhage, 69 $\pm$ 9 torr after administration of ketamine, and 68 $\pm$ 7 torr after administration of thiopental.

DISCUSSION

Moderate hemorrhage (30% blood loss) produced similar reductions in the anesthetic requirement of these two different intravenous anesthetic agents.

Many variables affect the amount of drug required to produce anesthesia.[7] We were not able to study all, or even most, of these variables because of limitations imposed by our experimental design, which was selected to give the best answer to the question posed (does hypovolemia reduce anesthetic requirement for induction agents, and if so, does the reduction differ for different drugs?) Consequently, we have limited physiological information from these animals to complement the finding of reduced anesthetic requirement.

We do have, however, a good deal of information about 21 other swine whose blood volume were similarly reduced (Weiskopf RB, Bogetz M, Roizen MF, Reid I: unpublished data). Variables in these animals were measured during normovolemia and after 30% blood loss. Mean values ($\pm$ SE) decreased for arterial blood pressure (from 129 $\pm$ 3 torr to 100 $\pm$ 6 torr) for cardiac output (from 174 $\pm$ 5 ml/min/kg to 113 $\pm$ 6 ml/min/kg), and for base-excess (from 5.7 $\pm$ 0.6 mmol/l to 3.3 $\pm$ 0.6 mmol/l); and increased for blood lactate concentration (from 1.10 $\pm$ 0.13 mmol/l to 1.69 $\pm$ 0.25 mmol/l). When half of the drug dose which produced anesthesia during normovolemia was administered to these animals during hypovolemia, further reductions occurred in cardiac output (to 76.9 $\pm$ 5.1 ml/min/kg after ketamine, and to 74.0 $\pm$ 5.9 ml/min/kg after thiopental), and in mean arterial blood pressure (to 41.4 $\pm$ 3.5 torr after

ketamine, and to 52.1 ± 7.8 torr after thiopental), and in base-excess. Blood lactate concentration increased even further. These mean arterial blood pressures are just below the level at which autoregulation is able to maintain normal cerebral blood flow. Thus, some of the decreased anesthetic requirement seen in these animals could have been a result of decreased cerebral blood flow. However, the animals in the present study had lesser decreases in blood pressure. Nor did they exhibit sufficient acidosis, hypercarbia, or decreased calculated oxygen content to account for a reduction of anesthetic requirement during hypovolemia.

We did not measure cerebral blood flow, and thus, cannot relate it to anesthetic requirement of these agents. However, since specific anesthetic site(s) of action are not known, knowledge of global cerebral blood flow would be of limited value. Knowledge of regional or microregional (if we knew which microregion) blood flow would be more helpful. Cullen and Eger related decrease in MAC to decreased oxygen delivery to the brain, either from decreased PaO_2[3] or severe isovolemic anemia[4]. A decrease in MAC correlates well with the occurrence of central acidosis[8]. Tanifuji and Eger found a 20% decrease in MAC for halothane in dogs made hypotensive to an arterial blood pressure of 40-50 torr by a combination of trimethaphan infusion, head-up tilt, and mild hemorrhage (approximately 12% blood loss)[9]. Rao *et al* [10] noted a decreased MAC for halothane in dogs made hypotensive by administration of pentolinium, trimethaphan, or nitroprusside, but stated that they did not find a correlation between decreased MAC and decreased carotid blood flow. In their experiments, mean arterial blood pressure did not fall below 60 mmHg, a level above that which autoregulation can no longer maintain cerebral blood

flow. MAC however, decreased during the administration of all three drugs; carotid blood flow did decrease significantly in the dogs given two of the drugs, but the large variability prevented achievement of statistical significance for those in the third group. Furthermore, in the dog, carotid blood flow is not a good indication of total cerebral blood flow. Thus, the literature does not contain a definitive study relating anesthetic requirement to cerebral blood flow.

Hemorrhage increases sympathetic activity[11] and circulating catecholamines in swine (Weiskopf RB, Bogetz M, Roizen MF, Reid I: unpublished data). Since an increase in sympathetic activity increases anesthetic requirement, it is possible that anesthetic requirement would be reduced further when the sympathetic response to hemorrhage is not possible or is blocked.

Our studies were performed with injectible agents and not inhalation agents. Thus, it is possible that some, or even all of the reduction in anesthetic requirement we observed after hypovolemia was due to a higher concentration of the drug in the blood and brain owing to a reduced volume of distribution. Changes in concentration of the drug at the site of action would depend upon alterations of blood flow to that site relative to differences in blood concentration.[12]

Price[13] predicted that following a single intravenous injection of thiopental, its concentration in the central nervous system would be higher after hemorrhage sufficient to reduce cardiac output by 40%, but insufficient to alter cerebral blood flow, than after a similar injection during

normovolemia. This mathematical model assumed that thiopental does not alter tissue blood flow. However, this is not true during hypovolemia. From Price's figure one would estimate that the hypovolemic condition he assumed would reduce the necessary dose of thiopental by approximately one-third. Our finding of a 33 $\pm$ 5% reduction in dose of thiopental is in accord with this, although in the other series of hemorrhaged swine in which we did measure cardiac output, it fell by 35%. Bergman[14], in hemorrhaged dogs, found a decreased plasma concentration of thiopental 5-90 minutes after injection over a 2 minute period. Thiopental, however, disappears very rapidly from plasma and richly perfused organs, such as brain. Five minutes after its administration, the concentrations of drug in the central pool and in the rapidly perfused viscera are less than 10% and 50% of their respective peak concentrations;[15] and 60 minutes after injection, concentrations in both compartments are less than 5% of their peak values.[15] Peak brain drug concentration and anesthetic effect occur within the first 2 minutes after injection. Because thiopental rapidly leaves the areas of interest, attempts to extrapolate from small concentrations measured much later, would be subject to error. This would be further compounded as the drug's effect on hemodynamics changed with changing concentrations in various compartments. Bergman did not measure the dogs' blood pressure or cerebral blood flow. It is possible that with the fall in blood pressure that likely occurred after thiopental administration to his hypovolemic animals, cerebral blood flow fell, thus decreasing washout of the drug, resulting in lower plasma concentrations. This is possible because within 15-45 seconds after injection concentration of the drug in richly perfused tissue is higher than in arterial

plasma.[15,16] Unfortunately, we did not measure drug concentrations in either plasma or brain, and thus, cannot confirm or refute Price's predictions or our speculations.

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Table 1. Minimal Anesthetic Dose of Ketamine and Thiopental in Swine during Normovolemia and after Hemorrhage

Drug	Minimum Anesthetic Dose (mg/kg) During Normvolemia	Minimum Anesthetic Dose (mg/kg) During Hypovolemia	Reduction in minimum anesthetic dose during hypovolemia (%)
Ketamine	17.50 ± 0.72	10.31 ± 0.60*	40 ± 5
Thiopental	11.25 ± 1.02	7.50 ± 0.72*	33 ± 5

Data are mean ± SE.

n = 4 per group

*Statistically different ($P < 0.05$) from normovolemic state.

Title: NITROUS OXIDE AND HALOTHANE CAUSE DECREASED CARDIAC OUTPUT AND LACTIC ACIDOSIS DURING HEMORRHAGE

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Introduction. Hemorrhage stimulates the sympathoadrenal system (1). Although anesthetic agents may cause further stimulation, it does not necessarily follow that this would be beneficial when inducing anesthesia during hypovolemia. When used for induction of anesthesia during hypovolemia, ketamine increases plasma catechols, but causes cardiovascular depression and systemic metabolic acidosis (2). Nitrous oxide has been used during hypovolemia because of its analgesic properties and mild sympathetic-like activity. We sought to determine whether at equivalent anesthetic concentrations, during hypovolemia the cardiovascular consequences of N_2O differed from those of an agent (halothane) with sympatholytic action.

Methods. Ten domestic swine (21.5±1.3kg) were each studied twice. Studies in each animal were separated by at least one week. The animals were anesthetized with halothane in O_2 and N_2 to allow for insertion of peripheral venous and systemic and pulmonary arterial cannulae. The trachea of each pig was intubated, the animal paralyzed with metocurine, and ventilated to maintain P_aCO_2 at 40 torr during all conditons. Administration of halothane was discontinued as each pig was studied supine, normovolemic, after end-tidal halothane concentration (measured by mass spectrometry) had decreased to less than 0.025 MAC. Measurements were repeated after blood volume reduction of 30% over 30 minutes. Anesthesia (chosen randomly) was then induced with 0.25 MAC halothane (Group I) or 0.25 MAC N_2O (Group II). One week later, the experiment was repeated using the other anesthetic agent. Measurements were repeated 5 min and 30 min after induction of anesthesia, 30 min after return of shed blood, and 60 min after elimination of the anesthetic. Results were compared by Student's t-test, accepting $p<0.05$ as statistically significant.

Results. 30% blood loss decreased right- and left-sided cardiac filling measures, mean systemic blood pressure, stroke volume, and cardiac output. Systemic vascular resistance, oxygen consumption, blood lactate concentration and plasma catecholamines increased (table 1). Before induction of anesthesia, there were no differences between the two groups. Five minutes after induction of anesthesia (Table 2), although Group II animals had higher plasma norepinephrine concentrations, the only other significant difference was a higher heart rate for Group II. Thirty minutes after induction of anesthesia, N_2O administration was associated with higher BPa, heart rate, SVR, and VO_2, but lower SV; there was no difference between groups for Q or blood lactate concentrations. After return of shed blood plasma catechol concentrations were higher in Group II; there were no other significant differences. After elimination of the anesthetic agents, there were no differences between the groups.

Discussion. We have found that induction of anesthesia in hypovolemic swine with N_2O further increases norepinephrine, but causes reduction in cardiac output and failure to meet oxygen demand as demonstrated by increased blood lactate concentration similar to that of halothane. We conclude that the sympathetic stimulation seen with N_2O is counterbalanced by its direct depressant effects, and that N_2O does not offer an advantage during hypovolemia over in comparison with an anesthetic that has sympatholytic properties.

Table 1
Response to 30% Hemorrhage in Anesthetized Swine

	Normovolemia	Hypovolemia	P
BPa (torr)	133±3	100±5	<0.001
Q_t ($ml O_2$/Kg/min)	192±5	121±6	<0.001
HR(beats/min)	128±6	182±9	<0.001
SV(ml/Kg)	1.55±0.07	0.69±0.05	<0.001
SVR(torr/4min)	33.7±1.5	40.3±2.2	<0.005
Lactate(mmol/L)	1.12±0.14	1.56±0.17	<0.02
$\dot{V}O_2$ ($ml O_2$/Kg/min)	7.74±0.27	8.74±0.37	<0.01
Epinephrine(pg/ml)	335±41	731±66	<0.001
Norepinephrine(pg/ml)	339±40	677±118	<0.02

Data are mean ± S.E.M.; n=10; BPa, mean systemic blood pressure; Q_t, cardiac output; HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance; $\dot{V}O_2$, oxygen consumption

Table 2: Response 5 Min After Induction of Anesthesia

	Group I	Group II	P
BPa	39±6	61±10	NS
Q_t	63±6	84±11	NS
HR	157±15	191±18	<0.05
SV	0.422±.043	0.447±.045	NS
SVR	28.7±2.9	36.4±4.3	NS
Lactate	2.88±0.46	2.28±0.26	NS
$\dot{V}O_2$	5.85±0.48	7.20±0.71	NS
Epinephrine	2507±527	2290±824	NS
Norepinephrine	423±88	1332±404	<.05

Table 3:Response 30 min After Induction of Anesthesia

	Group I	Group II	P
BPa	56±6	86±7	<0.02
Q_t	105±10	111±7	NS
HR	154±15	207±14	<0.001
SV	0.71±0.06	0.55±0.03	<0.05
SVR	26.1/-2.3	38.3±4.0	<0.02
Lactate	3.52±0.42	2.84±0.49	NS
$\dot{V}O_2$	7.60±0.57	8.86±0.60	<0.05
Epinephrine	1241±313	1592±623	NS
Norepinephrine	404±73	1203±337	<0.02

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Title: INDUCTION OF ANESTHESIA IN SWINE DURING HYPOVOLEMIA: COMPARISON OF HALOTHANE, ENFLURANE, AND ISOFLURANE

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Introduction. Although hypovolemia is usually corrected before the induction of anesthesia, the urgency of surgery may not permit this. The presence of hemodynamic instability then necessitates the use of a lower than usual dose of anesthetic. In fact, a patient may be given only oxygen and a muscle relaxant until some degree of cardiovascular stability is acheived. At that time, one would want to administer an anesthetic which has minimal effects on the compensatory mechanisms for hemorrhage. Since halothane, enflurane, and isoflurane have different cardiovascular effects during normovolemia, this study compared their effects when used to induce anesthesia during hypovolemia.

Methods. 30 domestic swine (20.2+/-0.4kg) were briefly anesthetized to allow the insertion of peripheral venous and systemic and pulmonary arterial cannulae. Each pig was intubated, paralyzed with metocurine, and mechanically ventilated to maintain PaCO2 at 40 mmHg. PaO2 was maintained at 150 to 210 mmHg. Administration of the anesthetic was discontinued and each pig was studied awake, supine, and normovolemic after the end-tidal anesthetic concentration (measured by mass spectrometry) had decreased to less than 0.05 MAC. Measurements were repeated after a blood volume reduction of 30% over 30 min. Each pig was assigned randomly to 1 of 4 groups for anesthetic induction while hypovolemic: halothane, enflurane, isoflurane, or no agent (control). Measurements were made 5 and 30 min. after the end-tidal anesthetic concentration reached and was stable at 0.4 MAC (0.5% halothane, 1.25% enflurane, 0.85% isoflurane); control animals were studied at a comparable time. Shed blood was then returned, the anesthetic was discontinued, and measurements were made 30 min. later. For each experimental condition, results among groups were compared using analysis of variance with repeated measures and Newman-Keuls' method of multiple comparisons. $p<0.05$ was accepted as statistical significance.

Results. There were no differences among the four groups in the normovolemic or in the awake, hypovolemic condition. 30% blood loss caused the expected cardiovascular and metabolic effects (table 1). Halothane, enflurane, and isoflurane caused similar cardiovascular effects when used to induce anesthesia during hypovolemia; all were different from control animals (table 1). Animals given enflurane had the highest blood lactate concentration. When shed blood was returned and the anesthetic was discontinued there were no differences among the three anesthetic and control groups. All animals survived.

Discussion. Although halothane, enflurane, and isoflurane have different cardiovascular effects during normovolemia (1,2,3), they caused a similar degree of cardiovascular depression when used to induce anesthesia during hypovolemia. Halothane did not preserve systemic vascular resistance and isoflurane did not preserve myocardial performance or cardiac output.

Enflurane caused the greatest imbalance of oxygen supply and demand as reflected by the highest lactate concentrations. All three volatile anesthetics interfered with the compensatory mechanisms for hemorrhage. Therefore, considerations other than the cardiovascular effects of these anesthetics should determine which of these drugs should be used when inducing anesthesia during hypovolemia.

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